The Journal of Allergy

VOL. 29 MAY, 1958 No. 3

Original Articles

ENZYMATIC MECHANISMS IN THE ACTION OF COMPLEMENT

POSSIBLE RELATIONS TO ALLERGY

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IN DISCUSSING the subject of enzymatic mechanisms of complement action, one unavoidable difficulty is that I shall have to say quite a bit about complement. Persons not in the field usually have the same attitude toward complement as that expressed by Albert Einstein when he was given a novel by Franz Kafka to read. When finished with the book, he was asked, "What do you think of it?" Replied Einstein, "Really, nothing in the universe is that complicated." As a preliminary, therefore, in order to dispel this attitude, I shall review briefly a little bit of our present knowledge of complement.

Complement is that mysterious group of substances which is involved in the lysis of sensitized red cells and certain bacteria; it is a necessary adjunct to the action of properdin; and it has been invoked with more or less success as the responsible agent in a number of bodily processes, including, as we shall later see, allergy. The earlier concept of the way complement acted in immune hemolysis was that one had an antibody to the red cell and that this antibody or hemolysin combined or "sensitized" the cell and then an entity, complement found in fresh unheated serum, took part in the lysis of the cell. It was found, however, by work stretching over twenty years or so that complement was not a single, simple "entity," that it could be divided into at least four parts or "components," and that all of the "components" were required in order for lysis to occur. Table I shows the manner in which these components have been named and defined. First we have complement (called, for brevity, "C'"). Then each of the components is given a number; the first component is C'1, the second component is C'2, etc. The first component, C'1, is the component which

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Presented at the annual meeting of the American Academy of Allergy, Los Angeles, California, Feb. 4, 1957.

Received for publication Feb. 19, 1957.

TABLE I. THE COMPONENTS OF COMPLEMENT AND THEIR PROPERTIES

COMPONENT		PROPERTIES
First	(C′1)	In precipitate of serum brought to pH 5.0-5.5 and low ionic strength; heat labile
Second	(C′2)	In supernatant of serum brought to low ionic strength and pH 5.0-5.5; heat labile
Third	(C′3)	Inactivated by the yeast preparation, zymosan; heat stable
Fourth	(C′4)	Inactivated by amines (e.g., ammonia, hydrazine); heat stable

is precipitated from serum when the concentration of salt is reduced by either dilution or dialysis and the pH is lowered to around 5; the second component, C′2, remains in the supernatant. Both the first and second components are destroyed by heating to 56 degrees. The third component, C′3, is the component inactivated by yeast or bacteria, or more usually by zymosan, a polysaccharide isolated from yeast by Pillemer and Ecker.[1] The fourth component, C′4, is the component which is inactivated by amines, such as ammonia or hydrazine.

It has been known for some time that these components act in a definite sequence and that, in addition to these components, calcium and magnesium ions (Ca^{++} and Mg^{++}) are required for hemolytic activity. The recent work of Levine and associates[2, 3, 4] has indicated more precisely the nature of this sequence of component action and has shown at what steps calcium and magnesium ions (Ca^{++} and Mg^{++}) are involved. Fig. 1 shows a summary of their work. Here the steps in the immune hemolytic reaction, as we know them today, are given. The first step, of course, is the sensitization step in which A (the antibody) combines with E (erythrocyte) to form the sensitized cell, EA.

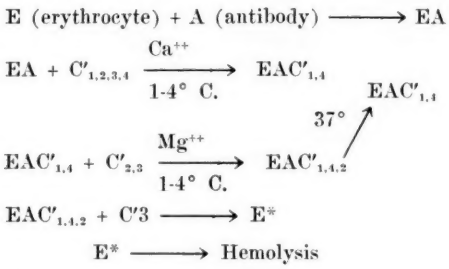

Fig. 1.—The course of the immune hemolysis reaction. (From the work of Levine and associates.[2-4])

The sensitized cell, EA, in the cold, in the presence of Ca^{++} but in the absence of Mg^{++}, combines with the first and fourth components to form the so-called 1,4 cell or $EAC'_{1,4}$. If the mixture is still kept cold and Mg^{++} is added, second component activity goes on the 1,4 cell, and one has the so-called 1,4,2 cell or $EAC'_{1,4,2}$. As long as the cells are kept cold the 1,4 or 1,4,2 cells can be washed free of excess complement and used as sources of the first, fourth, or second components. If the temperature is raised, say to 37 degrees, the second component activity is quickly destroyed and one has cells that have only first and

fourth component activity. If one takes the 1,4,2 cells, adds the third component (C'3), and raises the temperature, hemolysis occurs with neither Ca^{++} nor Mg^{++} being required.

Now this is all very intricate, but what meaning does it have for us as allergists? In attempting to answer that question, I shall restrict my attention to the types of allergy which experimentally, if not always clinically, can be transferred by serum and shall ignore the types transferrable by cells. With this restriction in mind, we can define allergy from the immunologic, if not the clinical, point of view, as the study concerned with the causes, nature, and consequences of the cellular and tissue damage induced by an antigen-antibody reaction. In the type of hypersensitivity with which allergists generally concern themselves, the cellular or tissue damage is manifested by the release of pharmacologically active substances such as histamine, serotonin, heparin, etc. In immune hemolysis, however, there is certainly cellular damage induced by an antigen-antibody reaction, and there seems to be no ground in logic for not looking upon it as essentially an allergic reaction. This logic, it should be noted, does not involve the idea that the mechanism of immune hemolysis is necessarily the same as the mechanisms of all the types of hypersensitivity in which circulating antibody is involved. Yet, because the immune hemolysis reaction is, from the experimental viewpoint, the simplest form of allergic reaction, it appeared to me that an investigation of the mechanism of complement action might very well serve as a model for the investigation of the more complex anaphylactic or atopic reactions.

In this investigation the working hypothesis used was that the activation of a proteolytic enzyme was involved in the action of complement. The choice of this working hypothesis was dictated by the knowledge that such a hypothesis had been advanced by a number of workers[5-9] to explain the tissue damage occurring in anaphylaxis. Little progress was made, however, until it was decided to investigate whether di-isopropyl fluorophosphate would inhibit complement action. The reason for this choice was as follows: Di-isopropyl fluorophosphate, or DFP as it is called, is one of the group of so-called "nerve gases" discovered by the Germans during World War II and intensively studied since. Di-isopropyl fluorophosphate was found to owe its very great toxic action to the inhibition in vivo of the enzyme involved in nerve conduction—acetylcholine esterase. Further work revealed that DFP and like substances were specific inhibitors not only of acetylcholine esterases but of esterases in general and that its action was restricted to this particular class of enzymes, that is, to enzymes which are capable of splitting esters into their constituent alcohol and acid. Moreover, it had been shown that DFP was capable of inhibiting the activity of those (and only those) proteolytic enzymes, such as trypsin and chymotrypsin, which were also esterases, that is, which could hydrolyze esters of certain amino acids. Thus, if it could be found that complement activity was inhibited by di-isopropylfluorophosphate, it could be considered very strong evidence indeed that an enzyme (or enzymes) was involved in complement action

and even more that the enzyme (or enzymes) involved was an esterase. However, before our investigation got under way, Dr. Lawrence Levine[10] informed me that inhibition occurred when DFP was added to a guinea pig complement-sensitized cell mixture in concentrations of from 10^{-3} to 10^{-2} M. I was quickly able to confirm this.[11, 12] In addition, the very curious and important observation was made that, in order for DFP to inhibit complement, sensitized red cells had to be present. If the sensitized cells were absent, DFP had no effect; I will return later to the interpretation of this finding.

On testing the dialyzed supernatants from a DFP-inhibited mixture of sensitized red cells and complement, it was found that only the first component of complement showed an appreciable decrease in activity. This suggested that it was the first component which was inhibited by di-isopropyl fluorophosphate. This was confirmed when it was found that only the first component activity was inactivated when cells containing the first, second, and fourth components were incubated with DFP.

It has been shown that di-isopropyl fluorophosphate inactivates esterases by having the di-isopropyl phosphate group combine irreversibly with the active group of the enzyme. However, Wilson and others have shown that certain compounds, such as nicotinohydroxamic acid can reverse this combination and also restore enzymatic activity. In fact, this finding is the basis for the work on these compounds as antidotes for nerve gas poisoning. Therefore, when it was demonstrated that nicotinohydroxamic acid reversed the DFP inactivation of the first component, it was clear that the DFP inactivation of C′1 is a specific inactivation. This being established, the conclusion followed that the first component is an esterase capable of being inhibited by DFP. In explanation of the need for sensitized cells to be present in order for DFP to be able to act, it was concluded that C′1 exists in serum in an inactive form as a proenzyme, a proesterase, which is not capable of being inactivated by DFP. In the presence of sensitized cells, however, it is changed to an active form, capable of being so inhibited. This behavior is the same as is known to occur with proteolytic enzymes, such as trypsin and chymotrypsin, which are inhibited by DFP, although the inactive precursors, trypsinogen and chymotrypsinogen, are not. The concept of C′1 existing as an inactive proenzyme which is activated by the antigen-antibody reaction is also the same conclusion reached in 1954 by Lepow and his co-workers[13] from an entirely different type of evidence.

Attention was then turned to an attempt to find the type of substrate upon which C′1 would act.[14] The investigation was guided by the belief that proteolytic enzyme activity is involved in immune hemolysis, the knowledge that some proteolytic enzymes are also esterases capable of splitting certain amino acid esters, and more directly by the finding of Troll and colleagues[15] that proteases of serum exist which are capable of hydrolyzing various amino acid esters. On employing sensitized cells containing the first, second, and fourth components of complement and many of the amino acid esters used by Troll and associates, it was possible to show a splitting of p-toluene sulfonyl L-arginine methyl ester by these cells but not by sensitized cells alone. Now p-toluene sulfonyl arginine methyl ester, also known as tosyl arginine methyl ester or

more curtly as TAMe, has the structure shown in Fig. 2. It is split by certain proteolytic enzymes, such as thrombin, trypsin, and plasmin, into methyl alcohol and tosyl arginine.

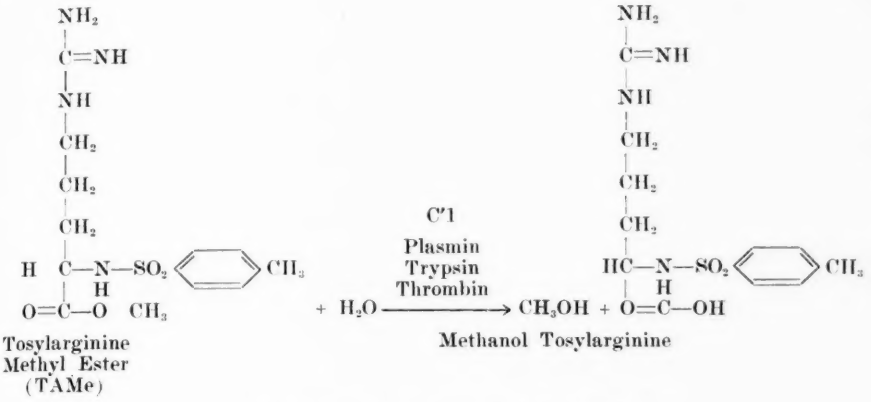

Fig. 2.—Enzymatic hydrolysis of TAMe.

On the basis of this reaction, it was possible to assay quantitatively the ability of these 1,4,2 cells to split TAMe. An assay of the C'1 activity of the same cells was also worked out. It was thus possible to correlate quantitatively the two activities of these cells. Before this was done, it was shown that the TAMe splitting activity of the 1,4,2 cells had all of the attributes of an enzymatic reaction; the splitting was linear with time and red cell concentration, it had a pH optimum between 7.0 and 8.0, and the relationship between substrate and velocity of hydrolysis followed quite precisely well-known laws of enzyme kinetics. It was then possible to show that when the complement activity of the guinea pig serum used to prepare the 1,4,2 cells was destroyed so that there was no C'1 activity on these cells, there also was no TAMe esterase activity. In addition, if one destroyed varying amounts of C'1 activity on these cells by the addition to them of varying amounts of DFP, one destroyed quantitatively corresponding quantities of TAMe esterase activity. If one tested 1,4,2 cells prepared with various rabbit hemolysins or red cells from various sheep prepared with the same hemolysin, the C'1 activity and the TAMe esterase activity were found to vary in quantitatively similar fashion. If the amount of guinea pig complement used to prepare the 1,4,2 cells was varied, both the C'1 and TAMe esterase activity varied in the same characteristic manner. There was no such correlation between the TAMe esterase and C'4 or C'2 activity of these cells.

An experiment based on the following reasoning was then set up to test more directly the hypothesis that the active group of TAMe esterase and C'1 were identical. The active group of C'1 is capable of binding DFP and, therefore, is inactivated; the enzymatically active group of TAMe esterase is capable of binding TAMe—this is how it is split. If the active groups responsible for these two functions are the same, then adding TAMe to the 1,4,2 cells before

adding DFP should block DFP from the active group and thus prevent the inactivation of C′1 by di-isopropyl fluorophosphate. This experiment was done, and it was found that, whereas the C′1 activity of the cells treated with DFP alone was completely destroyed, the C′1 activity of cells treated with DFP in the presence of TAMe was completely retained. Thus, from this experiment and the previously described experiments, it was concluded that the first component of guinea pig complement is a TAMe esterase. This is the same conclusion previously reached by Lepow and associates[16, 17] after studying partially purified human first component and eluates from antigen-antibody precipitates.

Since TAMe is known to be split only by proteolytic enzymes with esterase action, I suggested that C′1 might in addition be a proteolytic enzyme. In line with this suggestion, our laboratory has further shown that several amino acid esters and a number of peptides are capable of inhibiting the hemolytic activity of complement.[18] This work was started on the hypothesis that if the various components of complement are proteolytic enzymes, then synthetic compounds structurally related to the substrates of these supposed enzymes should be capable of inhibiting immune hemolysis by competing with the natural substrates. Three classes of compounds were found to be inhibitory: (1) derivatives of basic amino acids, such as lysine ethyl ester and TAMe; (2) sulfhydryl-bearing compounds; and (3) derivatives of aromatic amino acids. The finding that the presence of aromatic amino acids is required for the inhibition by peptides was taken as indicative of the possibility that one of the components of complement is a proteolytic enzyme requiring aromatic amino acids in its substrate.

What are the implications of the work on complement for allergy in general? In discussing this point, much of what will be said will, of necessity, be speculative. Yet such speculation, I hope, will give you some reason to share my faith that this "booming, buzzing confusion," which in this infancy of our knowledge is how the world of allergy must appear to us, will some day fall into ordered patterns.

The question naturally occurs as to whether or not complement might be responsible for the cellular damage seen in anaphylaxis. This possibility was first advanced by Friedberger and Hartoch[19] in 1909, denied by most, and recently revived by a number of investigators, including Schwab and colleagues,[20] Lange and associates,[21] Ungar and associates,[22] Lepow[13] and most recently Bier and co-workers.[23] In this connection, in light of the recent work concerning the importance of the mast cells as repositors of histamine and heparin,[24] it is attractive to speculate that in at least some species the release of heparin and histamine in anaphylaxis is a manifestation of mast-cell damage by an antigen-antibody reaction in the same way that hemoglobin liberation is a manifestation of red blood cell damage in immune hemolysis. This concept would imply that mast cells are capable of fixing antibody and that the cell, upon the reaction of this antibody with antigen, is capable of being damaged by complement. None of this is known, but there are available techniques capable of finding whether any of this speculation is true, and such investigations are being presently planned in my laboratory.

There is no reason, however, to believe that the mast cell necessarily plays the predominant role in every species and under every situation to which the term *anaphylactic shock* is applied. In rabbit anaphylaxis in general, the platelets[25] seem to play the role ascribed previously to the mast cell. In the reversed passive Forssman anaphylaxis in guinea pigs studied by Arbesman and associates,[26] among others, the so-called Forssman antigen is an integral part of the cells of the vascular endothelium as well as other sites,[27] and when the Forssman antibody is injected it combines directly with the antigen in these and the other cells. On the basis of the exact analogy with the situation in immune hemolysis, I think it overwhelmingly likely that complement plays a role in Forssman shock, which in all details is like the role it plays in immune hemolysis.[28-30] (This is the only place in the field of allergy where to me at present the likelihood does seem overwhelming.)

From the very meager evidence at hand, it is far from clear to what degree one has to postulate fixation of antibody on cells in order for shock to occur. I would not go so far as Bronfenbrenner[6] or Burdon[9] in postulating that the reaction is solely or wholly humoral. In fact, in guinea pig anaphylaxis and in human atopy I would cling to the orthodox position and consider it cellular. However, in another type of reversed passive anaphylaxis studied by Arbesman and his colleagues,[26] in which rabbit antibody to guinea pig serum is injected into guinea pigs, the site of the antigen-antibody reaction seems clearly to be in the blood. It is not known whether in this situation complement or the activation of anaphylatoxin so assiduously studied by Roche e Silva and Aronson[31] or the permeability factor of Miles and Wilhelm[32] is the humoral factor concerned. For that matter, the relationship of these three factors to each other is not clear at present.

For more than forty years claims have been made repeatedly that an enzyme (usually considered to be a protease) is activated by an antigen-antibody reaction.[5, 6, 8, 9] For almost that length of time these claims have been denied.[33, 34] The recent work on complement presents direct unequivocal evidence that in one place, at least, an antigen-antibody reaction is capable of changing an enzyme from an inactive to an active state. Similarly, it has been claimed that it is this activated enzyme which, in one way or another, is responible for the allergic signs and symptoms. Dénials have been equally vociferous, however, that if such activation occurs it plays little or no role in the allergic reaction.[35-37] It is clear, from the work described, that not only is an enzyme, C′1, activated during the course of immune hemolysis but that this activated enzyme takes a necessary part in the sequence of reactions leading to cellular damage. Moreover, it is a likely inference that C′1 is a protease, although admittedly there is no direct evidence on this point. The work on complement does not prove the protease activation theory of allergic reactions. However, it does provide comfort for those, like myself, who believe in the protease activation theory, not out of any great regard for either the quality or quantity of the evidence so far amassed in its support but more on the basis of its inherent plausibility and simplicity.

Leads to future work on the validity of the enzyme activation theory are suggested by the investigation of complement. Enzyme inhibitors have been employed to a small extent in the investigation of anaphylaxis.[38] From the work on complement it is clear that they might be further employed with even greater profit. The work on complement suggests that the view that the antigen-antibody reaction → enzyme activation → cellular damage should be substituted for by the viewpoint that the enzyme activation is itself a complex of reactions occurring in a rigid sequence. In attempting to unravel this postulated complex of reactions, the use of simple synthetic substrates might be profitably employed.

In viewing a given allergic reaction as a resultant of a complex sequence of events, of which the antigen-antibody reaction is only one part, one sees that the reaction can be prevented in a great number of different ways, many of which are quite nonspecific. For example, it has been found that when a guinea pig is sensitized to two antigens, of one which is antigenically weaker than the other, the response of the smooth muscle strip depend on the order in which the antigens are given. If the weaker antigen is given first, the strip will respond unimpaired to the subsequent addition of the stronger antigen. If, however, the stronger antigen is added to the strip first, the response to the addition of the weaker will frequently be absent.[39, 40] This nonreciprocal, nonspecific desensitization has its parallel in skin testing[41] and also in the "dominant antigen" concept of Cooke.[42] It is known that in immune hemolysis the reaction can come to a standstill because complement has been used up during the course of the immune hemolysis reaction in question or by another antigen-antibody reaction preceding the immune hemolysis. If one postulates that complement or a complement-like "tissue factor" is required for the allergic reaction, one can then offer an explanation of such nonreciprocal, nonspecific desensitization. The "better antigen," reacting first, uses up this "tissue factor" by virtue of its being a better antigen, leaving none available for the poorer antigen. The poorer antigen, reacting first, leaves sufficient hypothetic "tissue factor" to allow the better antigen to react. Obviously, this is not the only explanation possible. Bronfenbrenner[6] and Burdon[9] believe, for example, that an increase in protease inhibitor can account for this phenomenon.

Before bringing this discussion to a close, it should be stressed that it is of pressing concern not only to experimental allergists but even more especially to clinical allergists that this concept of "tissue factor" and especially proteolytic enzyme mediation of the immediate type of allergy to be proved or disproved. If it can be proved that enzymes are concerned in the reaction and if the specificity with which they work can be defined, then the way will be opened for a rational attack on the problem of the therapy of the clinical allergies. Let me again take our work on complement as a model. I mentioned that, based on the hypothesis that complement is made up wholly or in part of a group of proteolytic enzymes, we have found that several simple amino acid esters and simple peptides inhibited immune hemolysis. Lieutenant Wirtz,[43] an associate of mine, has definite evidence that certain of these inhibitors stop the immune

hemolysis reaction at different places. Moreover, on the basis of work done so far, it is possible to predict with a quite good degree of success from the structural formulae alone which compounds are likely to be inhibitors.

None of the compounds so far tested are sufficiently powerful inhibitors of complement to be of anything but academic interest. Nevertheless, the ideas leading to their discovery point the way to an approach to the therapy of allergic disease which may become possible when our knowledge of the biochemistry of the allergic reaction becomes sufficiently advanced.

While having no necessary relation to my thesis, it is, I think, of some interest that one of my associates, Dr. Barbaro[44] has shown that certain of the complement inhibitors will prevent the contraction of sensitized ileum and uterus induced by an antigen-antibody reaction to a greater extent than they will prevent the contraction caused by histamine. In addition, he has shown that certain of the complement inhibitors will also inhibit histamine release caused by an antigen-antibody reaction occurring in the presence of rabbit platelets.

I wish to take this opportunity to acknowledge publicly my debt of gratitude to Dr. Ben Z. Rappaport. In organizing the Allergy Unit at the University of Illinois, College of Medicine, of which I was formerly a member, his emphasis on the need for fundamental research in the field of allergy and his personal encouragement and support of my own attempts, he has truly stood *in loco parentis* as far as my research in allergy is concerned.

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COMPARISON OF INDUCED ELECTROLYTE DISTURBANCE IN NORMAL AND SENSITIZED GUINEA PIGS

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THE object of this work was to compare the response of sensitized and nonsensitized animals to factors which alter electrolyte equilibrium. The effects on tissue electrolyte content of two techniques which induce sodium retention and one which causes sodium depletion have been investigated.

METHODS

Groups of both sensitized and nonsensitized adult white guinea pigs (A.R.C. stock) with a body weight of 200 to 400 grams were subjected prior to death to one of three procedures which induce electrolyte disturbances. Groups of not less than five animals were used in each case.

Analysis of Muscles.—Animals were killed by a blow on the head. About 100 mg. of the tissue required was removed, wiped gently on filter paper to remove blood or mucus, and placed in a weighed glass tube which was then reweighed. Four muscles were studied—uterus, ileum, gastrocnemius, and diaphragm. The mucosa and endometrium of the ileum and uterus, respectively, were not removed. The muscles were dried for seventeen hours at 120° C. and weighed again one hour after removal from the oven. The tissues were dissolved in 1 ml. 50 per cent (V/V) nitric acid in a boiling water bath. This solution was diluted appropriately with distilled water for estimation of sodium and potassium by flame photometry. Duplicate estimations were always made.

Analysis of Serum.—Blood was withdrawn from the jugular vein after the animals had been stunned. Serum sodium and potassium were estimated by flame photometry after suitable dilution with distilled water.

Saturated Sodium Chloride Injection.—An injection of 0.2 ml. of saturated sodium chloride per 100 grams of body weight was given intraperitoneally a half-hour prior to death.

Administration of DOCA.—Daily sterile injections of 0.5 mg. (0.1 ml.) of DOCA in arachis oil were given intramuscularly to one of the four limbs in turn. Injections were continued for seven days, and the animals were killed twenty-four hours after the final injection. Control animals were treated with the hormone vehicle alone (0.1 ml.). With the sensitized animals, injections were arranged so that the animal would be killed twenty-one days after sensitization.

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This work was supported by a grant from the Asthma Research Council of Great Britain.
Received for publication Feb. 4, 1957.
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Intraperitoneal Glucose Injection.—An injection of 10 ml. of 5 per cent glucose solution per 100 grams of body weight was given intraperitoneally three hours prior to death. At death the intraperitoneal fluid was withdrawn by suction and analyzed for sodium and potassium content by flame photometry.

Sensitization Methods.—Except for the DOCA-treated animals, guinea pigs were sensitized by subdermal injection of 0.75 ml. of 10 per cent crystalline egg albumin solution under sterile conditions. Animals were killed twenty-one days later.

The DOCA-treated animals were passively sensitized by injection of 0.5 ml. rabbit serum intravenously, the rabbit having previously been sensitized with egg albumin. For this, we used a modification of Slavin's[5] technique, which involves using a calcium alginate gel as an antigen depot. An injection of 20 ml. of the following solution was given intraperitoneally to each rabbit:

5 Gm. crystalline egg albumin
5 Gm. sodium alginate
0.5 Gm. phenol
Distilled water to 100 ml.

This injection was followed immediately by 10 ml. of 2 per cent calcium chloride given into the same site. Three weeks later a booster dose of egg albumin was given intravenously, and after a further ten days blood was withdrawn for use.

A test for sensitization was made by adding a suitable dose of antigen to a bath containing Krebs solution in which was suspended a strip of ileum from the animal. The results from animals giving a negative response were excluded.

RESULTS

Effect of sensitization Alone on Composition of Serum and Muscles.—Figures given in Table I show that sensitization did not affect the water, sodium,

TABLE I

TISSUE OR FLUID	NO. OF ANIMALS	WATER (PER CENT)	SODIUM (MEQ./L. OR MEQ./100 GM. DRY TISSUE)	POTASSIUM (MEQ./L. OR MEQ./100 GM. DRY TISSUE)
Serum				
Nonsensitized	18		129.0 ± 3.3	8.5 ± 0.27
Sensitized	16		131.0 ± 0.77	8.8 ± 0.26
Uterus				
Nonsensitized	8	79.8 ± 0.32	35.3 ± 0.77	38.0 ± 0.56
Sensitized	12	80.7 ± 0.15	33.8 ± 0.62	39.2 ± 0.64
Ileum				
Nonsensitized	8	79.4 ± 0.65	24.6 ± 0.71	50.7 ± 1.23
Sensitized	11	80.0 ± 0.26	23.7 ± 0.65	51.4 ± 0.51
Gastrocnemius				
Nonsensitized	9	P<0.01 { 77.5 ± 0.15	11.4 ± 0.43	P<0.001 { 49.0 ± 0.66
Sensitized	11	>0.001 } 78.0 ± 0.09	10.6 ± 0.18	} 52.8 ± 0.56
Diaphragm				
Nonsensitized	9	P<0.01 { 76.3 ± 0.34	14.2 ± 0.46	P<0.001 { 42.2 ± 0.70
Sensitized	11	>0.001 } 77.3 ± 0.12	14.1 ± 0.21	} 45.9 ± 0.36

The differences between the paired figures not bracketed can be accounted for by chance (P > 0.05).

or potassium content of serum or of smooth muscles. On the other hand, sensitization did appear to alter the total potassium content of striated muscles, significantly higher values being obtained in the sensitized group. In addition, the total water contents of the diaphragm and gastrocnemius were greater in the sensitized animals.

Effect of Administered Saline on Nonsensitized Animals.—Injection of saturated saline solution caused a significant uptake of sodium in all tissues investigated. Reference to Table II shows that serum sodium content rose

TABLE II. SODIUM CONTENT OF TISSUES (MEQ./100 GM. DRY TISSUES AND MEQ. PER LITER)

TISSUE	NORMAL	AFTER GLUCOSE	AFTER NaCl	AFTER DOCA	AFTER OIL
			Nonsensitized Animals		
Uterus	35.3 ± 0.77	28.9 ± 0.57*	41.1 ± 1.10*	36.8 ± 0.63*	32.2 ± 0.61
Ileum	24.6 ± 0.71	22.1 ± 0.62*	30.9 ± 1.80*	26.1 ± 0.14*	20.9 ± 0.67
Gastrocnemius	11.4 ± 0.43	10.5 ± 0.55	14.7 ± 0.64*	13.0 ± 0.61*	9.2 ± 0.37
Diaphragm	14.2 ± 0.46	12.9 ± 0.41*	18.9 ± 0.70*	14.5 ± 0.71	13.0 ± 0.45
Serum	129.0 ± 3.3	133.0 ± 4.4	169.0 ± 2.6*	141.0 ± 3.1	134.0 ± 2.2
			Sensitized Animals		
Uterus	33.8 ± 0.62	—	—	34.8 ± 0.57*†	36.8 ± 0.48
Ileum	23.7 ± 0.65	19.5 ± 0.40*†	29.9 ± 2.27*	22.7 ± 0.51†	22.3 ± 0.49
Gastrocnemius	10.6 ± 0.18	8.5 ± 0.24*†	10.9 ± 0.16†	11.1 ± 0.24†	10.7 ± 0.18
Diaphragm	14.1 ± 0.21	11.0 ± 0.37*†	15.2 ± 0.24*†	13.7 ± 0.34	13.4 ± 0.25
Serum	131.0 ± 0.8	125.0 ± 2.8*	145.0 ± 2.6*†	127.0 ± 1.5†	127.0 ± 0.70

*Significantly different from its own control ($P = < 0.05$) (for example, nonsensitized tissue after glucose treatment compared with normal nonsensitized value, or sensitized tissue after DOCA treatment compared with value of sensitized tissue after arachis oil treatment).

†Significantly different from corresponding nonsensitized tissue ($P = < 0.05$) (for example, value of sensitized tissue after NaCl treatment compared with nonsensitized tissue after NaCl treatment).

from 129 to 169 mEq. per liter a half-hour after the saline injection and that the sodium content of all the muscles was increased significantly. In addition the muscle potassium content was increased (Table III). There was no change, however, in total water content of the muscles (Table IV).

TABLE III. POTASSIUM CONTENT OF TISSUES (MEQ./100 GM. DRY TISSUE OR MEQ. PER LITER)

TISSUE	NORMAL	AFTER GLUCOSE	AFTER NaCl	AFTER DOCA	AFTER OIL
			Nonsensitized		
Uterus	38.0 ± 0.56	42.7 ± 0.56*	42.5 ± 0.60*	39.5 ± 0.28	39.7 ± 0.48
Ileum	50.7 ± 1.23	51.4 ± 1.26	54.0 ± 0.78*	46.3 ± 0.81	47.2 ± 0.86
Gastrocnemius	49.0 ± 0.66	54.6 ± 0.71*	55.1 ± 0.67*	49.4 ± 0.32	48.5 ± 0.79
Diaphragm	42.2 ± 0.70	43.2 ± 0.81	46.9 ± 0.56*	42.5 ± 0.51	42.0 ± 0.45
Serum	8.5 ± 0.3	6.8 ± 0.9	7.4 ± 0.7	8.6 ± 0.4	8.6 ± 0.7
			Sensitized		
Uterus	39.2 ± 0.64	—	—	41.6 ± 0.71†	40.4 ± 0.53
Ileum	51.4 ± 0.51	48.2 ± 0.40*†	48.6 ± 1.27*†	52.3 ± 0.84†	50.8 ± 0.53
Gastrocnemius	52.8 ± 0.56	52.0 ± 0.57†	51.5 ± 0.60†	50.8 ± 0.53†	50.3 ± 0.51
Diaphragm	45.9 ± 0.36	44.1 ± 0.37*	43.8 ± 0.43*†	44.8 ± 0.47†	45.0 ± 0.48
Serum	8.8 ± 0.3	9.1 ± 0.7	7.9 ± 0.4	8.7 ± 0.3	8.5 ± 0.4

*Significantly different from its own control ($P = < 0.05$) (for example, nonsensitized tissue after glucose treatment compared with normal nonsensitized value).

†Significantly different from corresponding nonsensitized tissue ($P = < 0.05$) (for example, value of sensitized tissue after NaCl treatment compared with nonsensitized tissue after NaCl treatment).

Effect of Saturated Saline Injection on Sensitized Animals.—The serum sodium level of sensitized animals was raised from 131 mEq. per liter to 145 mEq. per liter a half-hour after the saline injection (Table II). This increase

of only 14 mEq. per liter was in striking contrast to the elevation of 40 mEq. per liter which had been found in nonsensitized animals. This difference in response cannot be accounted for by chance ($P<0.001$). Following the same pattern, the concentration of sodium within the muscles of sensitized animals was considerably less than that which had occurred in nonsensitized animals. Furthermore, the uptake of potassium by the muscles was less in the sensitized group (Table III) and the two striated muscles showed a lower water content (Table IV).

TABLE IV. PERCENTAGE WATER CONTENT OF TISSUES

TISSUE	NORMAL	AFTER GLUCOSE	AFTER NaCl	AFTER DOCA	AFTER OIL
			Nonsensitized		
Uterus	79.9 ± 0.32	79.5 ± 0.31	79.0 ± 0.27	79.9 ± 0.02	79.8 ± 0.29
Ileum	79.4 ± 0.65	78.6 ± 0.29	78.9 ± 0.32	78.0 ± 0.02	77.8 ± 0.40
Gastrocnemius	77.5 ± 0.15	78.0 ± 0.21	77.5 ± 0.22	76.8 ± 0.02	76.5 ± 0.02
Diaphragm	76.3 ± 0.34	76.5 ± 0.41	76.6 ± 0.15	74.9 ± 0.02	75.2 ± 0.02
			Sensitized		
Uterus	80.7 ± 0.15	—	—	81.0 ± 0.34†	81.4 ± 0.12
Ileum	80.0 ± 0.26	79.5 ± 0.19†	79.6 ± 0.28	79.8 ± 0.23†	79.4 ± 0.24
Gastrocnemius	78.0 ± 0.09	78.1 ± 0.16	76.3 ± 0.13*†	77.6 ± 0.22†	77.6 ± 0.14
Diaphragm	77.3 ± 0.12	77.1 ± 0.15	75.8 ± 0.16*†	76.8 ± 0.25†	76.8 ± 0.21

*Significantly different from its own control ($P = < 0.05$).

†Significantly different from corresponding nonsensitized tissue ($P = < 0.05$) (for example, value of sensitized tissue after DOCA compared with nonsensitized tissue after DOCA treatment).

From preliminary studies, it appeared that in sensitized animals the peak of sodium elevation in the tissues occurred one quarter of an hour after the saline injection. This peak was maintained at a similar level at one-half hour and one hour. The nonsensitized animals, with their greater response, required one-half hour to attain maximum sodium uptake in the tissues. There was a slight falling-off of effect after one hour. These results show that using a time interval of one-half hour in the main experiments was justified, since the maximum response in both groups was evidenced at this point.

Effect of DOCA Administration on Nonsensitized Animals.—DOCA treatment (0.5 mg. DOCA in arachis oil daily for seven days) caused a slight increase in serum sodium level from 134 mEq. per liter to 141 mEq. per liter. In three out of the four muscles investigated there was a highly significant increase in sodium content (P values of <0.001, $<0.01>0.001$, and <0.001). The hormone vehicle, arachis oil, itself had some effect in causing a fall in muscle sodium content.

DOCA administration did not affect the potassium or water content of the muscles significantly.

Effect of DOCA Administration on Sensitized Animals.—There was little appreciable response of sensitized animals to DOCA administration. The serum sodium level remained constant, and only one out of the four muscles investigated showed a significant increase in sodium ($P<0.02>0.01$). DOCA had no effect on the potassium or water content of the muscles.

Thus, once again there was a striking difference in the responses of sensitized and nonsensitized animals. Statistical analysis of the results shows that the sodium content of both serum and muscles was significantly less in the sensitized group as compared with the nonsensitized group. Sensitized animals appeared to have a higher muscle potassium content, but this is partly attributable, in the gastrocnemius and the diaphragm, to the higher initial content resulting from sensitization alone. The sensitized group also showed a significantly higher muscle water content (Tables II, III, and IV).

Effect of Glucose Injection on Nonsensitized Animals.—It was found that three hours after glucose administration the muscles had become depleted in sodium. There was a net flux of sodium into the peritoneal fluid, such that its concentration approached that of serum. Figures given in Table II show that the total sodium content of each of the muscles investigated had fallen appreciably but serum sodium was not significantly changed. The concentration of sodium in the withdrawn fluid was 96.5 mEq. per liter, showing an influx of sodium into the peritoneal cavity of 9.3 mEq. per kilogram of body weight. The volume of fluid withdrawn was the same as that which had been injected (22.4 and 22.3 ml.). There was no change in the percentage water content of the muscles (Table IV).

The concentration of potassium in the intraperitoneal fluid was 2.92 mEq. per liter, thus showing an influx of 0.27 mEq. potassium into the peritoneal cavity per kilogram of body weight. Serum concentration showed no significant change, but there was some tendency for the muscles to take up potassium; two out of the four muscles showed a significant increase. This was possibly a compensatory increase toward balancing the sodium depletion.

Effect of Glucose Injection on Sensitized Animals.—The response of sensitized animals to this treatment was qualitatively similar to that of nonsensitized animals in so far as the muscles lost sodium. This effect was considerably exaggerated in sensitized animals, however; for instance the sodium content of diaphragm fell by 15 per cent (14.1 to 11.0 mEq. per 100 Gm. dry tissue), whereas that of nonsensitized animals fell by only 9 per cent (14.2 to 12.9 mEq. per 100 Gm. dry tissue). None of the differences in muscle sodium contents of the sensitized and nonsensitized animals could be accounted for by chance.

A further difference between the two groups was that muscles of sensitized animals tended to lose potassium, whereas those of nonsensitized animals showed an increase. Hence, the sensitized group showed a far greater electrolyte depletion than did the nonsensitized, the sodium loss was greater, and the compensatory potassium increase was not in evidence. In both groups, however, despite considerable change in sodium content, the total water content of the muscles remained essentially unchanged.

As with nonsensitized animals, glucose treatment did not significantly affect the sodium or potassium content of serum.

Analysis of the withdrawn intraperitoneal fluid revealed a significantly greater influx of potassium into the cavity in sensitized animals (0.35 mEq. per kilogram of body weight compared with 0.29 for normal animals, $P = 0.05$).

Sensitized animals also appeared to show a slightly greater influx of sodium (10.6 mEq. per kilogram of body weight compared with 9.3 for normal animals), but this difference can be accounted for by chance. In sensitized animals the amount of fluid recovered was slightly greater than that injected.

DISCUSSION

Effect of Sensitization on Tissue Sodium and Potassium Content.—The results have shown that sensitization alone caused no disturbance in the sodium or potassium content of either serum or smooth muscles. Surprisingly enough, striated muscles of sensitized guinea pigs were found to have higher potassium contents than those of normal nonsensitized animals. Both diaphragm and gastrocnemius showed significantly higher potassium and water concentrations but no significant change in sodium content. These results have been shown to be repeatable.

Some previous workers have reported electrolyte changes occurring in tissues during sensitization. Einbinder, Nelson, and Fox[1] reported that the main electrolyte shifts occurring in mice are that potassium and sodium are deposited in the bones. They reported a fall in sodium content of "viscera" (pooled heart, liver, spleen, and lungs). In mice there appears to be no uptake of potassium by skeletal muscle as was found in the present work on guinea pigs. This is possibly due to species variations, which is further evidenced by the fact that the *normal* potassium content of skeletal muscles in these two species is grossly dissimilar (393 mEq. per kilogram of wet tissue for mouse compared with 490 for guinea pig).

Further species differences in the response to sensitization are indicated in analysis of blood. Wenner and Buhrmester[6] reported a striking elevation of serum potassium in rabbits, whereas in guinea pigs no change occurs. Nevertheless, sensitization is associated with some electrolyte disturbances in all three species on which reports are available.

Comparison of Nonsensitized With Sensitized Animals' Response to Induced Electrolyte Disturbance.—It has been shown that sensitized animals responded to a *lesser* extent than did nonsensitized animals to factors causing an increase in body sodium (DOCA or saline treatment), the tissue sodium content being elevated to a lesser extent. On the other hand, sensitized animals showed a *greater* response to sodium depletion (induced by injecting glucose solution), that is, the tissue sodium level fell to a greater extent.

The results have shown that muscles of sensitized animals lose sodium more readily than those of nonsensitized animals when electrolyte depletion is induced. On the other hand, they take up less sodium when the total body sodium is increased. Two of the techniques used involved intraperitoneal injection of a solution which served to alter the composition of the blood and surrounding tissues. It is possible, although not proved, that the passage of water and electrolytes into and out of the peritoneal cavity proceeds at different rates in the sensitized and nonsensitized animals.

DOCA treatment was ineffective in raising tissue sodium level in sensitized animals, although the dose used did cause sodium retention in nonsensitized guinea pigs. A possible explanation may be that sensitized animals develop refractoriness to DOCA more readily than do normal animals. It has been shown previously that a completely refractory state can be induced in animals with repeated injection of sodium-retaining hormones, including DOCA.[2-4] For instance, using a "DOC beef adrenal protein mixture," these workers demonstrated complete refractoriness appearing as early as the fourth injection. Further evidence is required, however, to establish whether or not a shorter period of DOCA treatment than that used in the present experiments can cause sodium retention in sensitized animals and, hence, whether or not this refractoriness plays a significant role.

Another factor which may account for the differences found between sensitized and nonsensitized animals is that the mechanism controlling the intracellular concentration of electrolytes in the muscle is disturbed in sensitized animals. The high total potassium content found in striated muscles of untreated sensitized animals is possibly due to a high intracellular concentration, since serum level (and thus, presumably, extracellular concentration) remained normal. Since intracellular potassium concentration is so much greater than extracellular potassium, fluctuation in intracellular content would greatly influence the results of total muscle potassium.

Alternatively, the control of renal excretion of electrolytes may be disturbed in sensitized animals. For instance, if there were a relative lack of sodium-retaining hormones in sensitized animals, then a sodium load in the body would be lost more readily than normal. Hence, the blood and muscle sodium concentration would be lower in such animals. Conversely, if the body were depleted of sodium, then these animals could less readily correct this by retaining more sodium. This is in accordance with the results reported. In addition, some disturbance in factors controlling electrolyte balance could account for the high muscle potassium concentration found in two muscles of untreated sensitized animals.

SUMMARY

1. Estimations of water, sodium, and potassium content of uterus, ileum, gastrocnemius, diaphragm, and serum have been made on nonsensitized and actively sensitized guinea pigs. Sensitized animals were killed twenty-one days after antigen injection. It was found that neither the smooth muscles nor serum showed any differences in the two groups but the striated muscles of sensitized animals had an abnormally high potassium content.

2. Groups of normal and either actively or passively sensitized animals were subjected to electrolyte disturbance prior to death. Tissue analyses revealed that increasing the tissue sodium content (by intraperitoneal injection of saturated saline solution, 0.2 ml. per 100 grams of body weight, a half-hour prior to death or by seven daily injections of 0.5 mg. DOCA) caused a lesser uptake of sodium in sensitized animals than in normal animals.

3. On the other hand, the response of sensitized animals to a depletion of total body sodium (by intraperitoneal injection of 10 ml. of 5 per cent glucose solution per 100 grams of body weight three hours prior to death) was greater than normal.

4. Some factors which may contribute to an explanation of these results are discussed.

DOCA used in this study was kindly supplied by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

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REPEATED MULTIPLE FRACTURES OF RIBS BY COUGH IN BRONCHIAL ASTHMA

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FRACTURE of the ribs in bronchial asthma has been reported in the literature on two previous occasions. One of these occurred in status asthmaticus and involved the first rib.[1] The other involved two ribs anteriorly, with no recurrences.[2] The present case revealed repeated fractures of ribs, both anteriorly and posteriorly, on three occasions, during a period of eight years. Rib fractures occurred following cough in 1949, 1955, and 1956. During the first episode of severe asthma and cough (1949), the fractures were not recognized on a routine chest film, and the final diagnosis was bronchial asthma with pleurisy. During the second episode (1955), special roentgenograms of the ribs revealed fractures. During the third episode (1956), the patient recognized the similarity of the pain to that experienced in 1955, and special roentgenograms revealed the fractures.

Fractures of the ribs due to cough have been reported as early as 1834.[3] They have been seen in pulmonary tuberculosis,[4] whooping cough,[5] atypical pneumonia,[6] bronchosinusitis,[7] epidemic tracheitis,[8] pregnancy,[9] and paroxysmal cough following laryngeal aspiration of a foreign body.[10] Because of the lack of appreciation, in textbooks and the literature, of fracture of the rib as a complication of cough in bronchial asthma, it was thought that the following case would be significant and interesting.

CASE REPORT

A 65-year-old man entered the Santa Rosa Hospital for a sixth time on Dec. 12, 1956. He complained of severe pain in the right posterior chest. The pain had started three days prior to admission, during a mild episode of wheezing, severe cough, and infection.

Bronchial asthma had been diagnosed in Nebraska in 1948. The patient had come to Texas to avoid the severe winter weather. He was first hospitalized on Dec. 7, 1948. A roentgenogram of the chest revealed no abnormality. He was discharged on April 4, 1949, and was readmitted five days later, on April 9, because of wheezing and severe cough with pain in the chest. A chest film on May 7, 1949, revealed fractures of the eighth rib posteriorly on the right and healed fractures of the sixth and seventh ribs on the left in the anterior axillary line. On June 8, 1951, the patient was admitted for prostate surgery, and a chest film revealed that the old fractures had healed. On Dec. 17, 1955, he was admitted to the hospital with severe right chest pain, dry cough, and nasal obstruction. The admission diagnosis was pleurisy, right chest. A routine roentgenogram of the chest (Fig. 1) revealed no fracture. Because of the continuous pain, a flat plate of the abdomen was made. This included a portion of the lower ribs (Fig. 2), which showed a fracture of the ninth rib on the right posterior axillary line. The patient was again admitted to the

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Received for publication June 24, 1957.

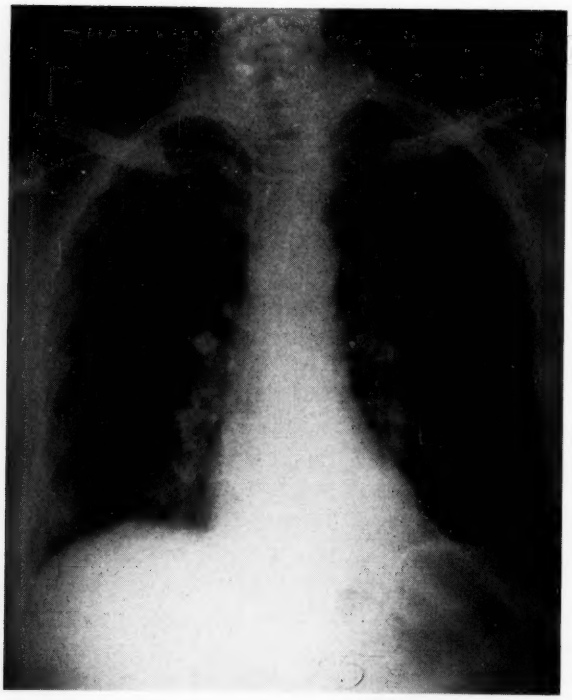

Fig. 1.—Posteroanterior roentgenogram of the chest showing no evidence of rib fracture. Dec. 17, 1955.

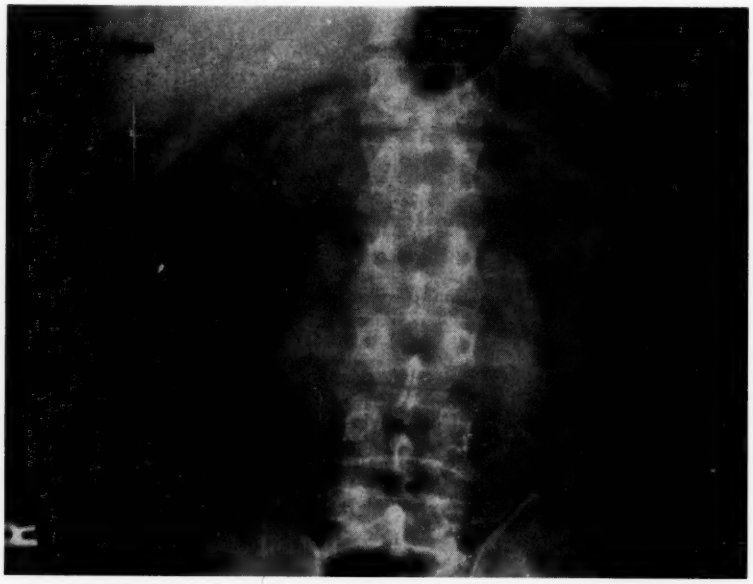

Fig. 2.—Flat plate of the abdomen showing lower ribs with fracture of the ninth rib on the right posterior axillary line. Dec. 19, 1955.

hospital on June 14, 1956, with gastrointestinal discomfort and nausea. A complete examination was done, including electrocardiogram, excretory urogram, an upper G.I. study, and chest film. The findings were nonulcerative duodenitis and large esophageal hernia. The patient was again admitted on Dec. 16, 1956, for severe pain in the right chest. He had stated that he had had a similar episode of pain one year before and that a fractured rib had been found. He had been under our care for bronchial asthma and nasal polyps since May 2, 1956, and had responded well to hyposensitization therapy. He was found to be very sensitive to mountain cedar and stated that a Christmas tree had started this episode of severe coughing.

Fig. 3.—Special roentgenogram for ribs showing fractures of the eighth and ninth ribs on the right posterior axillary line. Dec. 17, 1956.

Physical examination revealed a blood pressure of 138/70 mm. Hg, pulse 76, and respiration 24. The patient was in obvious pain and would speak only in a whisper. There was marked tenderness on slight pressure over the right chest in the posterior axillary line at the level of the eighth rib. There was no dullness, and the breath sounds were harsh. The heart was normal in size and no murmurs were heard. The abdomen was soft, and the liver and spleen were not palpable. Laboratory studies revealed a hemoglobin level of 12 gm. per 100 c.c. and a hematocrit of 38. Clotting time was six minutes. There were 6,700 white blood cells per cubic millimeter with a normal differential count. The cardio-Kline and Mazzini tests were nonreactive. The serum phosphorus, serum calcium, and serum phosphatase were normal, and the cultures were negative for acid-fast bacilli. An electrocardiogram revealed occasional premature auricular extrasystoles. A special chest film on Dec. 17, 1956, revealed fractures of the right eighth and ninth ribs in the posterior axillary line (Fig. 3).

Because of marked sensitivity to adhesive tape, his chest was immobilized with an elastic belt and sedatives were given. The restraining belt relieved the condition considerably. The patient was treated with analgesics and support for one week. Subsequent chest films (March 17, 1957) showed the fractures to be healed and in good alignment (Fig. 4).

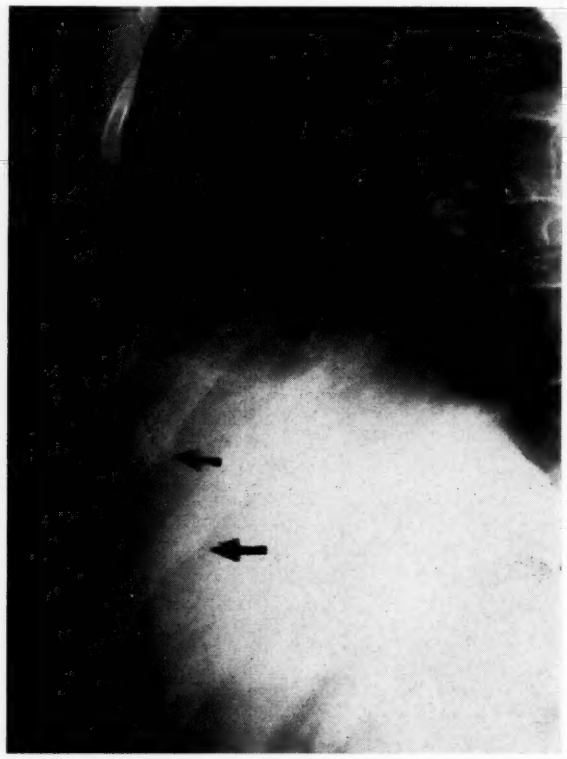

Fig. 4.—Special roentgenogram for ribs showing healing of fractures of the eighth and ninth ribs on the right posterior axillary line. March 18, 1957.

COMMENT

Cough fractures have been reported as a complication of bronchial asthma in only a few instances.[1, 2] No case of repeated occurrence of fractures has previously been reported. In the case presented here there was no evidence of calcium or metabolic disease and the symptoms were similar to those of pleurisy. Marked tenderness over the site of the fracture was the most significant sign. A history of a similar episode of pain one year before was the only clue.

SUMMARY

Fracture of the ribs due to severe cough in bronchial asthma should be considered when pain in the chest is present. Excessive chest pain occurring in bronchial asthma should lead one to obtain special chest films for ribs.

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AEROSOLIZED STEROIDS IN BRONCHIAL ASTHMA

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CORTISONE and drugs related to it are extremely valuable in the management of asthma. Unfortunately, there are some patients who require treatment with large doses of these drugs for long periods, and the undesirable effects of steroids become a problem in management. Since the therapeutic application of certain corticosteroids directly to the inflamed skin and eye is effective, their application directly to the bronchial tree as an aerosol might permit certain cases of asthma to be controlled with a total dose of steroid small enough to avoid the hazards of systemic hypersteroidism.

Several attempts have been made to use steroids topically in asthma. Gelfand[1] administered cortisone as an aerosol produced from a suspension in saline. The beneficial effect noted in four out of five cases may have been due to systemic absorption, since the amount nebulized was 50 mg. daily. British workers[2] administered a dry powder of hydrocortisone in a dose of 7.5 mg. per day or 15 mg. per day. Improvement was noted in eleven of fifteen patients and persisted as long as three weeks, despite substitution of a placebo. This study had the disadvantage of not being rigidly controlled. Other workers,[3] using the double-blind technique* gave hydrocortisone hemisuccinate as an aerosol in a dose of 15 mg. per day from an aqueous solution. Patients receiving a placebo did as well as those receiving hydrocortisone, and the authors concluded that hydrocortisone was ineffective as an aerosol in chronic asthma.

We have been interested for several years in the topical application of steroids but have not been convinced that we were able to administer aerosol in sufficient amounts to be effective topically without producing effects due to systemic absorption. Recently new preparations of steroids which seem promising and which might make it possible to determine whether or not steroids are effective topically in asthma have become available. The following studies consist of two parts. In the first, prednisolone was compared with a placebo under controlled conditions using the "double-blind" technique. In the second, hydrocortisone was evaluated clinically without controls.

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Received for publication March 12, 1958.

*Administration of a placebo and one or more preparations to be evaluated under circumstances in which neither physician nor patient knows the identity of the preparation given.

METHODS OF ADMINISTRATION OF AEROSOLIZED STEROIDS

In essence, the objective was to deliver to the surface of the airway an amount of steroid, as yet undetermined, which would be effective and yet would not constitute a therapeutic dose if given by mouth. The smallest quantity of steroid which is capable of producing a therapeutic effect in asthma when absorbed systemically is equivalent to approximately 30 to 40 mg. of hydrocortisone in twenty-four hours. Ideally, therefore, the total daily dose administered by aerosol should fall well below this, and of this total dose, a significant (though as yet undetermined) quantity must reach the airway. Borrowing from experience with the steroid drugs used in the eye, on the skin, and in joints, one would expect that only a small amount would be required but that for optimum effectiveness this should be present continuously over a period of days.

In the light of these considerations, an aerosol should meet the following specifications: (1) the concentration of the steroid to be nebulized should be sufficient to permit administration of an effective dose in a relatively brief period so as not to make undue demands on the subject; (2) the size of the particles or droplets should be small enough that impingement on the tongue and oropharynx will be minimized and particles will enter the bronchial tree in sufficient amounts; (3) the preparation should be tolerable as to taste and should not be irritating on inhalation.

Suspensions of finely divided particles of prednisolone and hydrocortisone in Freon* delivered through a metered valve and plastic adapter appeared to meet these conditions.

These preparations contained a dispersing agent to stabilize the suspension and prevent plugging of the metered valve. We were informed[4] that with each depression of the valve, 0.25 mg. of prednisolone and 1.6 mg. of hydrocortisone was delivered, respectively, from the opening of the 1 inch adapter provided by the manufacturer. In an attempt to reduce oral impingement, experiments were carried out with a 14 inch transparent plastic tube with an internal diameter of 1 inch attached to the adapter, and air flowing from the aperture in the back of the adapter through the tube at a rate of 1 liter per minute. Approximately 50 per cent of the steroid delivered was deposited on the wall of the tube within the first 6 inches of the adapter, whereas only a trace was deposited in the distal half of the tube. This experiment suggested that a substantial portion of the steroid delivered from the adapter would be deposited on the tongue and oropharynx and, therefore, would be available for systemic absorption without exerting any topical effect on the airway. Because the role of topically applied steroid would be difficult to assess if the amount swallowed were to approach a quantity that might favorably influence asthma, deposition of the aerosol in the mouth was minimized in the first part of the study by having the patient inhale the aerosol through a plastic tube of the dimensions just described. In the course of time, large quantities of material

*Medihaler-Cort. kindly supplied by J. W. Stutzman, M.D., of Riker Laboratories.

were deposited on the walls of these tubes. The use of the plastic tube unquestionably decreased the dose of steroid administered, but it had the desirable effect of increasing the proportion entering the airway as compared with that retained in the mouth. The decrease in the amount administered with each inhalation could be compensated for by increasing the number of inhalations. Though wasteful of drug and cumbersome for the patient, this arrangement was felt to be essential if such benefit as might occur were to be ascribed to a topical effect.

Estimation of Dose Administered.—We selected a patient who had been receiving steroids for several years because of severe intractable asthma and who had been shown to have no spontaneous adrenal activity as judged by blood and urinary steroid levels. Steroids were omitted for twelve hours and then blood levels were determined before and at intervals after the inhalation of hydrocortisone aerosol produced from a 12 mg. per milliliter suspension through a 14 inch tube.[5] By comparing the blood levels thus obtained with those obtained under similar circumstances following the intravenous and oral administration of 5 mg. of hydrocortisone, it was estimated that, after 50 inhalations of this material, approximately 2 mg. of steroid was absorbed systemically. If these data apply, then in the controlled study (Part I), in which thirty-six inhalations per day of a suspension containing 5 mg. of prednisolone per millimeter were taken, approximately 0.7 mg. was absorbed per day. This is probably well below the dose which would be effective in asthma if given by mouth.

Although a suspension of prednisolone was used in the controlled study (Part I), supplies of this material were limited. We felt that hydrocortisone would be as effective if used in equivalent dosage. The inhalation of aerosol through a 14 inch tube was not suitable for the routine treatment of most patients. In the second part of the study, therefore, patients were given hydrocortisone suspension through a 1 inch adapter. In order not to be confused by oral absorption, we limited the total daily dose to an amount which we believed too small to be effective orally in asthma.

Suspensions containing 30 mg. per milliliter and 15 mg. per milliliter were used initially, but in most instances a suspension containing 12 mg. per milliliter was used. The estimated daily dose was 18 mg. or less, and in most instances three to six inhalations of the 12 mg. per milliliter suspension were taken five times daily.

METHOD OF EVALUATION

Because of the variability in the course of asthma, it is difficult to evaluate the effect of a therapeutic agent in an individual patient unless that effect is either prompt or pronounced. With measures that exert their influence over a long period of time, we feel the double-blind technique to be highly desirable. The type of patient in whom an evaluation is made is also important. The value of a therapeutic measure can be clearly demonstrated in severe asthma

only if it is very effective, whereas in mild asthma one may gain the impression that any agent is effective. Because of the tendency for asthma to fluctuate widely in severity, it is difficult to select suitable patients for study. During any period of observation asthma tends to become either too severe or too mild to permit evaluation of a therapeutic agent.

After using an aerosol of prednisolone on a few patients, we gained the impression that it was therapeutically effective when six inhalations were taken six times per day from a Medihaler containing 5 mg. per milliliter of prednisolone suspended in Freon. We then proceeded to test this impression with rigid controls.

It was felt that the effect of steroids administered as an aerosol could best be demonstrated by giving the aerosol to patients who were being treated successfully with oral steroids. If the dose of oral steroids is reduced, there will be a tendency for asthma to recur. Under these circumstances, there should be less tendency for recurrence in a group receiving aerosolized steroid, if effective, than in a group receiving a placebo. Therefore, in the first part of the investigation only patients receiving oral steroids were selected for study. In order to obtain comparable groups, sixteen patients were paired on the basis of similarities in age, sex, and severity of disease.

According to the toss of a coin, one member of each pair was given the placebo suspension and the other was given the suspension of prednisolone. This was done by a technician and a physician who took no part in the subsequent management and evaluation of the patient. Although the two preparations were indistinguishable in appearance, the steroid suspension had a more bitter taste. Identification of the preparation on this basis was successfully prevented by telling the patients that they might notice a bitter taste and by deliberately avoiding subsequent discussion of taste.

Patients were instructed to take six inhalations six times per day and, if possible, to reduce their oral dosage of steroid every three days by 25 per cent or by ½ tablet per day, whichever was greater. In the meantime, they continued to use ancillary medication as needed.

The patients were seen at intervals of one week or less by physicians who were ignorant of which preparation the patients were receiving. The intensity and severity of symptoms were noted and the amount of ancillary medication was recorded. Expirograms (kymographic tracings of maximum forced expiration) were done at each visit. Each trial was carried on for one month or until relapse occurred. At the end of this period the efficacy of each preparation was rated.

In the second part of the study patients were followed in the same manner as those in the first part except that no placebo was given.

PART I. RESULTS OF CONTROLLED STUDY WITH PREDNISOLONE

Of the patients selected, three were deemed unsatisfactory for evaluation before any attempt was made to rate the effectiveness of the preparation that

they were receiving. Of the thirteen remaining patients, six were considered to have obtained a therapeutic effect (Table I). In every instance in which the preparation was deemed effective it proved to be prednisolone. Where the preparation was deemed ineffective it was prednisolone in one instance and placebo in six. The probability of such a distribution occurring by chance, based on the x^2 test, is less than 0.02. A high degree of statistical significance can therefore be ascribed to these results.

TABLE I

PREPARATION	EFFECT	NO EFFECT
Prednisolone	6	1
Placebo	0	6
	6	7

$$\Sigma x^2 = \frac{(6.0 - 3.24 - 0.5)^2}{3.24} + \frac{(3.76 - 1.0 - 0.5)^2}{3.76} + \frac{(2.78 - 0 - 0.5)^2}{2.78} + \frac{(6.0 - 3.22 - 0.5)^2}{3.22} = 6.42 \therefore p = <0.02$$

Before it was known which preparation was given, the course of treatment was analyzed. Four of the six patients receiving the placebo worsened in ten days or less, whereas with the steroid aerosol only one worsened during this period (the patient who was rated as having no effect).

One patient receiving placebo did not worsen during the period of study. Before we knew which preparation she was getting, however, the preparation was not deemed effective because the patient had stopped using it without worsening. On the other hand, two preparations were rated as effective despite a relapse late in the course of treatment. In these instances, prior to relapse, the patients had tolerated a lower dose of oral steroid than they had been able to tolerate for some time, and following relapse they responded slowly only to relatively large doses of prednisone by mouth.

PART II. RESULTS WITH HYDROCORTISONE

A total of forty-seven courses of treatment in thirty-nine patients with asthma have been evaluated. In thirty-one courses treatment was rated as effective, in seven ineffective, and in nine we could not decide. Further evidence that a local therapeutic effect was achieved is provided by a few patients who developed weakness and aching (symptoms suggestive of adrenal insufficiency) as oral steroid was withdrawn, but who did not suffer an increase in asthma. This occurred in three instances. These patients had similar difficulty previously when attempts were made to withdraw oral steroids, but in the past these symptoms were always accompanied by severe asthma which compelled us to reinstitute treatment. Such a sequence of events is illustrated by the following case report.

A 37-year-old white married woman had asthma for seven years. For six years she had been treated almost continuously with steroids or ACTH. Whenever the daily dose of

steroid was reduced below the equivalent of 40 to 50 mg. of hydrocortisone, asthma would recur and would be uncontrollable with bronchodilator drugs. In June, 1956, the last attempt to withdraw oral steroids resulted in asthma, weakness, and joint pains as the daily intake of prednisone was reduced from 10 mg. to 7.5 mg. The dose of prednisone was increased to 30 mg. per day but asthma did not completely disappear for about ten days. The dose was then reduced gradually to 12.5 mg. per day and maintained at that level until May 9, 1957. At this point the patient was given steroids by aerosol (fifteen inhalations daily of a suspension containing 30 mg. per c.c.) and oral steroids were reduced to 10 mg. per day. Her asthma became worse after one week, but when the number of inhalations of steroid aerosol was increased to 24 per day her asthma disappeared. She was then able to tolerate a reduction in oral dose to 5 mg. per day of prednisone over the course of the next two weeks, and simultaneously a suspension containing 12 mg. per milliliter was substituted. At this point she developed weakness, aching in the bones, and itching of skin with desquamation. No further reduction in dose was made for two weeks. The aching, itching, and weakness disappeared and the oral dose was then reduced further to 2.5 mg. per day over the course of the next 2 months without recurrence of symptoms. On Sept. 1, 1957, her oral dose was decreased from 2.5 mg. to 1.25 mg. daily. Weakness and pains in the joints again recurred but improved after three to four days. She remained well for two weeks and then suffered a recurrence of asthma. At that time 20 mg. of prednisone was given by mouth daily, the aerosol was discontinued, and the patient gradually improved.

Another situation which supports the topical effectiveness of hydrocortisone aerosol occurred in a 36-year-old woman who had both rhinitis and asthma. Both of these had been controlled with intermittent oral steroids along with bronchodilators and antihistaminic drugs. Asthma had always been the compelling reason for giving steroids. When she was given steroids by aerosol and oral steroids were withdrawn, asthma did not recur, but she developed severe nasal obstruction and headache which cleared when she was again treated with steroids in tablet form.

DISCUSSION

In previous studies reporting benefit from steroids given by aerosol, lack of adequate controls and the administration of amounts which would be effective if absorbed systemically make the conclusions questionable. We feel that the results of the double-blind trial indicated that prednisolone given as an aerosol exerted a therapeutic effect in asthma and, because of the precautions taken to reduce oral impingement, that this effect is a topical one on the bronchial mucosa.

In drawing conclusions from the uncontrolled study of hydrocortisone aerosol, we are on less firm ground. We have the impression that the aerosol was effective. As our experience increased, the impression became stronger. Furthermore, we found that in the group of patients under treatment we used very much less steroid in the form of tablets. Unless we were giving patients more steroid than necessary previously, this alone suggests effectiveness.

Even if a therapeutic effect can be attributed to the hydrocortisone aerosol, since with the short adapter a considerable amount must impinge in the mouth, it is possible that oral absorption accounted for an important part of the effect.

We estimate that the total amount delivered from the end of the short adapter was below 18 mg. per day. Were these amounts absorbed without acting topically, it is unlikely that a therapeutic effect would occur.

The most noticeable subjective effect reported by patients was a relief of cough and irritation, and some patients felt better even though there was little change in pulmonary function. This may be explained by greater deposition of steroid in the larger-caliber tubes of the bronchial tree where inflammation may lead to irritation and cough rather than obstruction to the flow of air.

Even after the question of effectiveness is settled, the clinical usefulness of this therapeutic measure is yet to be established. We have no way of knowing whether we are achieving a maximal topical effect. We would estimate that the therapeutic effect observed in the patients receiving hydrocortisone aerosol was only equivalent to that obtainable with approximately 40 mg. per day taken by mouth. This dose is insufficient to control many instances of severe asthma and may account for the poor results observed when patients with severe asthma were treated with aerosol alone. Although many patients complained of the bitter taste, the aerosol was acceptable to most. Removal of some of the coarse particles by baffling or some other measure may improve acceptability, cut down oral absorption, and permit a larger topical dose to be administered without giving enough orally to be of significance. A solution rather than a suspension may prove to be a better means of applying steroid to the bronchial tree.

When bronchial obstruction is severe it may be impossible to deliver enough aerosol to the more distal portions of the bronchial tree. Furthermore, particulate matter may be irritating when the asthmatic process is at its height. We have the feeling that the chief place of steroid aerosols will be in maintenance therapy rather than in the treatment of the acute exacerbation. Since there is relatively little hazard to short-term steroid therapy, there is little need to limit systemic absorption in these instances. The demonstration that steroids are at least somewhat effective should stimulate more vigorous study of the problem.

SUMMARY

Preparations of prednisolone and hydrocortisone suspended in a Freon propellant were administered as aerosols to asthmatic patients. Using the double-blind technique, we obtained strong evidence for a topical therapeutic effect of prednisolone in asthma. Clinical experience indicated that this was also true for aerosolized hydrocortisone. The topical therapeutic effect of steroids as given appeared to be approximately equivalent to a daily dose of 40 mg. of hydrocortisone by mouth.

Addendum: Since this paper was completed another study,[6] also using the double-blind technique, has appeared which indicates that hydrocortisone given as an aerosol can have a topical effect in asthma.

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PREDNISONE AND PREDNISOLONE IN CHRONIC ALLERGIC DISEASES

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THIS study is a follow-up of a previous one completed at the Institute of Allegy in 1955.[1] At that time only eight patients with bronchial asthma had been treated for only four weeks. No side effects were found during that time. The dosage of prednisone* and prednisolone* necessary for symptomatic relief was one-half to one-third that of hydrocortisone, with which these patients had been treated previously.

This present article covers treatment of fifty-eight patients. Thirty-seven had asthma, nine had seasonal rhinitis, four had perennial rhinitis, and eight had dermatitis. These patients were followed for from seven weeks to sixteen months. All patients were being treated with specific injection therapy, sympathomimetics, antibiotics, and any other symptomatic therapy necessary. Table I gives a summary of pertinent data of our findings.

In the group of thirty-seven asthmatic patients asthma was, for the most part complicated by other diseases: pulmonary fibrosis (2), dermatitis (1), pulmonary emphysema (1), hyperplastic sinusitis (8), arteriosclerotic heart disease (3), eosinophilic granuloma (1), esophageal diverticulosis (1), perennial rhinitis (3), hypertension (1), hay fever (1), and duodenal ulcer with subtotal gastrectomy done prior to administration of steroids.

It is significant that 73 per cent of these patients were over 40 years of age and the remaining 27 per cent were between 20 and 40 years of age. In all of these patients the asthma was either purely infective (35 per cent) or had an infective element to a great extent (65 per cent); the latter were usually more difficult to manage than the purely inhalant type of asthma.

Eighty-five per cent of these patients had their disease for more than five years, and only one had been ill for less than one year.

In spite of the severity and chronicity of the disease, 80 per cent of the patients were controlled with 15 mg. or less of prednisone or prednisolone per day, 11 per cent required 20 mg. or less, and only 9 per cent needed 20 to 40 mg. per day. All medication was given in divided doses.

Only four patients had any side effects; two had moon facies and peripheral edema, one had edema and an increase in hypertension, and the fourth had moon facies alone. By careful adjustment of sodium intake, good control was maintained without stopping therapy.

From the Institute of Allergy, Roosevelt Hospital.
Received for publication Feb. 20, 1957.

*Meticorten and Meticortelone used through the courtesy of the Clinical Research Division of the Schering Corporation, Bloomfield, New Jersey.

TABLE I

NO.	AGE	DURATION	ASTHMA: INHALANT	ASTHMA: INFECTIVE	ASSOCIATED ALLERGIES	COMPLICATIONS	PREDNISONE OR PREDNISOLONE THERAPY: DURATION	DAILY DOSE (MG.)	SIDE EFFECTS
					Asthma				
1	32	6 yr.	x	x	Hyperplastic sinusitis	0	7 mo.	10-15	0
2	53	4 yr.	x	x	Perennial rhinitis	0	7 mo.	15	0
3	50	29 mo.	0	x	0	Pulmonary fibrosis Partial blindness Emphysema	9 mo.	20-40	Edema Moon-facies
4	69	18 mo.	x	x	Hyperplastic sinusitis	Esophageal diverticulosis	6 mo.	10-15	0
5	66	16 yr.	0	x	0	Eosinophilic granuloma Arterioselerotic heart disease and failure	5 mo.	15-30	Edema,
6	56	11 yr.	x	x	0	0	7 mo.	5-10	0
7	41	4 yr.	0	x	Hyperplastic sinusitis	0	6 mo.	15	0
8	63	16 yr.	x	x	Hyperplastic sinusitis	0	2 mo.	2.5-5	0
9	70	29 yr.	x	x	0	0	8 mo.	15-20	0
10	40	5 yr.	x	x	Right antral polyp	0	3 mo.	15	0
11	42	39 yr.	x	x	0	0	4 mo.	5-10	0
12	59	9 yr.	0	x	0	0	4 mo.	5-10	0
13	37	5 yr.	x	x	0	0	8 mo.	2.5-5	0
14	25	3 yr.	x	x	0	0	6 mo.	5-10	0
15	59	7 yr.	x	x	0	Cor pulmonale	7 mo.	10-15	Moonfacies
16	44	7 yr.	x	x	0	0	5 mo.	5-20	0
17	33	7 yr.	0	x	0	0	15 mo.	10-15	0
18	32	32 yr.	0	x	Perennial rhinitis	0	3 mo.	10	0
19	27	22 yr.	x	x	Dermatitis	0	6 mo.	10	0
20	64	44 yr.	x	x	Hyperplastic sinusitis	Pulmonary fibrosis Emphysema	8 mo. 5 mo.	15	0
21	20	13 yr.	x	x	Perennial rhinitis	0		5-10	0
22	57	18 yr.	0	x	Hyperplastic sinusitis	0	7 mo.	15	0
23	23	11 yr.	x	x	0	0	5 mo.	5-15	0
24	41	12 yr.	0	x	0	0	16 mo.	15-20	0
25	44	7 yr.	0	x	0	0	4 mo.	5-20	0
26	41	12 yr.	0	x	Hyperplastic sinusitis	0	16 mo.	10-30	Moonfacies Edema
27	69	20 yr.	x	x	0	0	8 mo.	15	0
28	30	9 yr.	x	x	0	0	8 mo.	5-10	0
29	45	38 yr.	x	x	0	0	11 mo.	10-15	0
30	59	15 mo.	x	x	Hay fever	0	12 mo.	10-15	0

(Table I continued on next page.)

TABLE I—(CONT'D)

NO.	AGE	DURATION	ASTHMA		ASSOCIATED ALLERGIES	COMPLICATIONS	PREDNISONE OR PREDNISOLONE THERAPY		
			INHALANT	INFECTIVE			DURATION	DAILY DOSE (MG.)	SIDE EFFECTS
31	58	6 yr.	0	x	0	Arteriosclerotic heart disease Old coronary infarct	7 mo.	5-15	0
32	72	40 yr.	x	x	0	0	1.5 mo.	10-15	0
33	44	6 yr.	0	x	0	0	14 mo.	10-15	0
34	76	3 yr.	x	x	0	0	12 mo.	10	0
35	65	19 yr.	0	x	0	0	14 mo.	10-20	0
36	53	4.5 yr.	0	x	Polyps ethmoid	0	8 mo.	10-15	0
37	56	20 yr.	x	x	0	0	13 mo.	5-15	0
					Perennial Rhinitis				
1	66	12 yr.	0	x	Hyperplastic sinusitis	0	15 mo.	5-15	0
2	55	10 yr.	x	x	Nasal polyps	0	4 mo.	5-10	0
3	54	11 yr.	0	x	0	0	8 mo.	15	0
4	55	36 yr.	x	x	0	0	8 mo.	10-15	0
					Seasonal Rhinitis				
1	46	29 yr.	x	0	0	0	12 wk.	5-10	0
2	26	10 yr.	x	0	0	0	5 wk.	10	0
3	44	18 yr.	x	0	0	0	4 wk.	10	0
4	30	6 yr.	x	0	0	0	6 wk.	10	0
5	20	4 yr.	x	0	0	0	4 wk.	5	0
6	46	5 yr.	x	0	Asthma	0	6 wk.	15	0
7	40	15 yr.	x	0	Asthma	0	4 wk.	15	0
8	55	15 yr.	x	0	0	0	5 wk.	5	0
9	34	13 yr.	x	0	0	0	4 wk.	10	0

NO.	AGE	DURATION	DISTRIBUTION	ASSOCIATED ALLERGIES	COMPLICATIONS	THERAPY AS ABOVE		
						DURATION	DOSE (MG).	SIDE EFFECTS
				Allergic Dermatitis				
1	35	35 yr.	Hands and face	0	0	8 mo.	10-20	0
2	46	9 mo.	Generalized	0	0	8 mo.	5-10	0
3	45	45 yr.	Hands and face	0	0	7 mo.	10-20	0
4	2	23 mo.	Generalized	0	0	3 mo.	5-10	0
5	60	9 mo.	Hands, face, and elbows	0	0	5 mo.	5-10	0
6	32	6 yr.	Generalized	Perennial rhinitis and hay fever	0	12 mo.	5-10	0
7	20	18 mo.	Generalized	0	0	3 mo.	15	0
8	30	15 mo.	Generalized	0	0	7 mo.	10	0

In the remaining twenty-one patients who had seasonal rhinitis, perennial rhinitis, or chronic dermatitis, control was attained in thirteen on 10 mg. or less of prednisone or prednisolone. Eight were controlled on 10 to 20 mg. per day. No side effects were found in this group.

DISCUSSION

The data presented generally confirm the conclusions made by Skaggs, Bernstein, and Cooke,[1] namely, that good clinical response was obtained with relatively small doses of prednisone and prednisolone. Skaggs and associates did not note edema or elevation of blood pressure in the short time their patients were being treated. In our series, in which the period of treatment was much longer, relatively few cases showed a slight degree of moon facies and peripheral edema.[3] One case had some increase in pre-existing hypertension. None of the side effects were severe enough to stop therapy. Other authors[2-8] have described side effects in addition to those encountered in our series; these included epigastric pain, osteoporosis, duodenal ulceration of the gastrointestinal tract, increased appetite, insomnia, euphoria, mental overstimulation, excessive perspiration, muscle cramps, nausea, vomiting and diarrhea, and weakness. There was one case of severe depressive psychosis.

SUMMARY AND CONCLUSIONS

1. In thirty-seven cases of poorly controlled severe chronic bronchial asthma good results were obtained on small maintenance doses of prednisone and prednisolone.

2. In thirty of the cases of asthma (81 per cent) control was maintained with 15 mg. or less per day. The remaining seven (19 per cent) were controlled with 20 to 40 mg. per day.

3. Satisfactory response to the drug was not influenced materially by the presence of complicating diseases, age, duration of symptoms, or severity of the disease itself.

4. Excellent results were obtained in cases of chronic dermatitis, perennial rhinitis, and seasonal rhinitis with smaller doses than were required for the asthmatic patients. No side effects were observed in these patients. There were strikingly fewer complicating diseases noted in these three types of allergic conditions.

5. Side effects noted in this series occurred in four cases of asthma; the effects included only peripheral edema in three, with moon facies in three plus an increase in hypertension in one. In each case the side effects were only mild and did not require cessation of the drug. These patients were all over 40 years of age; their symptoms were of long duration, and three of them had particularly serious complicating diseases.

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TREATMENT OF RAGWEED HAY FEVER WITH METHYLPREDNISOLONE (MEDROL)

Comparative Effectiveness of Methylprednisolone* and Prednisolone**

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SINCE the introduction of cortisone for the treatment of ragweed pollinosis in 1950[1] continuing research has resulted in the use of increasingly more potent steroids with decreasing side reactions. The use of hydrocortisone, prednisone, and prednisolone in succeeding years in the therapy of allergic diseases resulted in lower doses with less untoward effects. Methylprednisolone, an analog of hydrocortisone similar to prednisolone except for the substitution of a methyl group for a hydrogen atom at the sixth alpha position (Fig. 1), has been shown in animals[2, 3] to be three times as potent as prednisolone by both the oral and subcutaneous routes. To determine clinically the relative potency of methylprednisolone to prednisolone, similar groups of patients with ragweed hay fever were chosen. These patients all lived in the same general environment and thus, in almost all instances, were exposed to the same amount of pollens on the same day.

PROCEDURE

One hundred thirty-one patients who either had responded poorly to courses of hyposensitization or had received no previous treatment were used in this study. Of these, forty-four were placed on prednisolone, forty-two on Medrol, and forty-five were used as controls. The latter were allowed to take any medication necessary, except the corticosteroids, for symptomatic relief. A previous study[4] had shown that 20 mg. of prednisolone a day was adequate to give at least 75 per cent relief in seventy-five out of seventy-nine patients. Since Medrol was presumed to be one-third more potent, a dosage of 15 mg. per day of each drug was arbitrarily chosen. The study was conducted by the double-blind method. Neither the doctor, the nurse, nor the patient knew which drug was given or received. The steroids were distributed in vials containing twenty-one tablets of 5 mg. each. Each vial was numbered from 1 to 150. A master list showing the assignment of drugs to numbers was available only to the statistician. Once started on a preparation, the patient was con-

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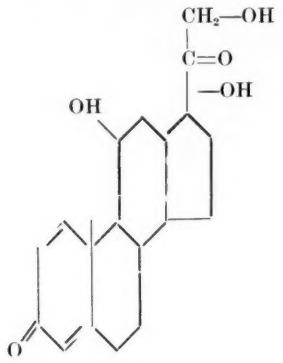
Received for publication Jan. 6, 1958.

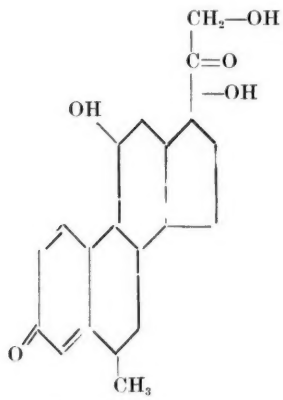
*Supplied as Medrol by the Medical Division of the Upjohn Company, Kalamazoo, Michigan.

**Supplied as Delta-Cortef by the Medical Division of the Upjohn Company.

tinued on the same medication throughout this period of study. In all cases, diagnosis of ragweed pollinosis was confirmed by history and intracutaneous tests. Hyposensitization therapy was continued throughout the study in those patients who had been seen prior to June, 1957. Each patient was given a card as described in a previous study[4] to record his symptoms. In this way a daily tabulation of symptoms (severe, moderate, slight, or none) was recorded. Each patient was required to return weekly for a week's supply of medication and to exchange the old vial for a new one with the same number.



Prednisolone



Methylprednisolone

Fig. 1.

At this time the quantity of unused tablets remaining in the vial was noted, unknown to the patient, and a copy of each patient's report of symptoms was transcribed to a master list. As each patient completed his course of treatment, his card was collected and an IBM card was punched. The data were then tabulated from those punch cards.

Each group contained approximately an equal number of male and female patients ranging from 10 to 69 years of age, with an average age of 33.

RESULTS

As was to be expected patients on either methylprednisolone or prednisolone had fewer days with severe symptoms than the control group. All patients had more severe symptoms when the pollen count was at its height (Fig. 2), but on days with lower pollen counts the group on methylprednisolone was more comfortable than either the prednisolone group or the control

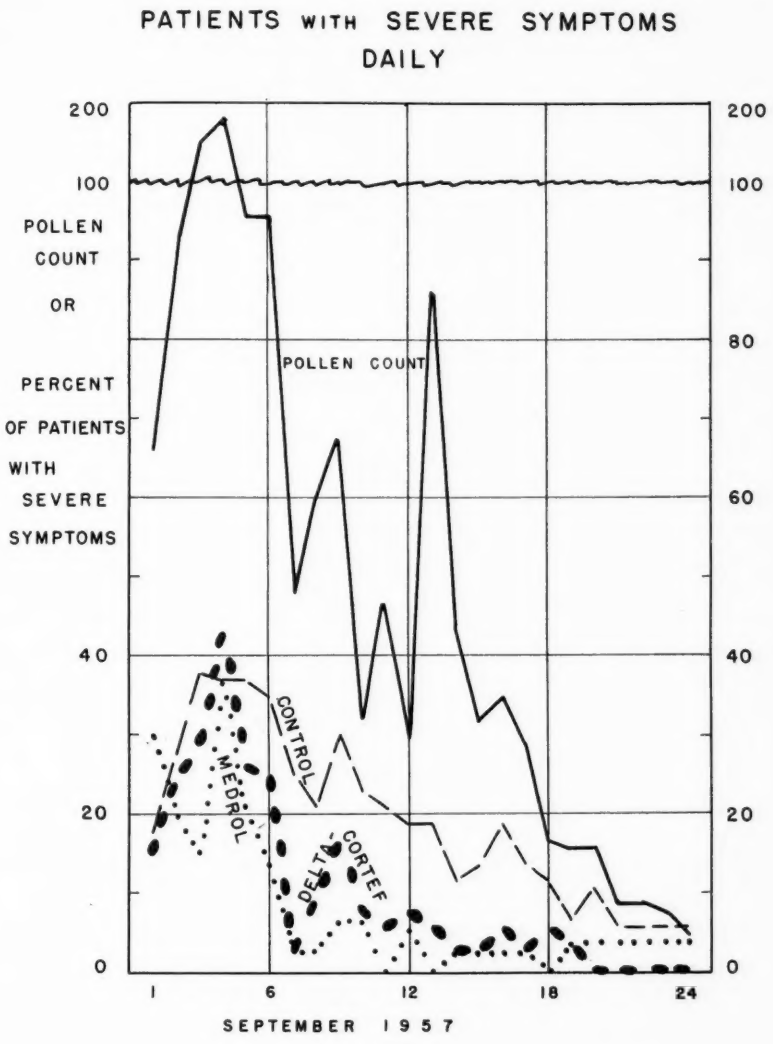


Fig. 2.

group. It is apparent that 15 mg. daily of either drug is inadequate to control symptoms caused by pollen counts over 80. Below this count this dosage was adequate. In all probability, doubling the dosage would abolish the symptoms in these cases.[5] As a corollary, the number of days each group of

patients had no symptoms was charted (Fig. 3). The group on methylprednisolone had more symptom-free days than the prednisolone or control group, but here again when the pollen count was at its height there was no difference between the groups. Despite the fact that patients were instructed to take

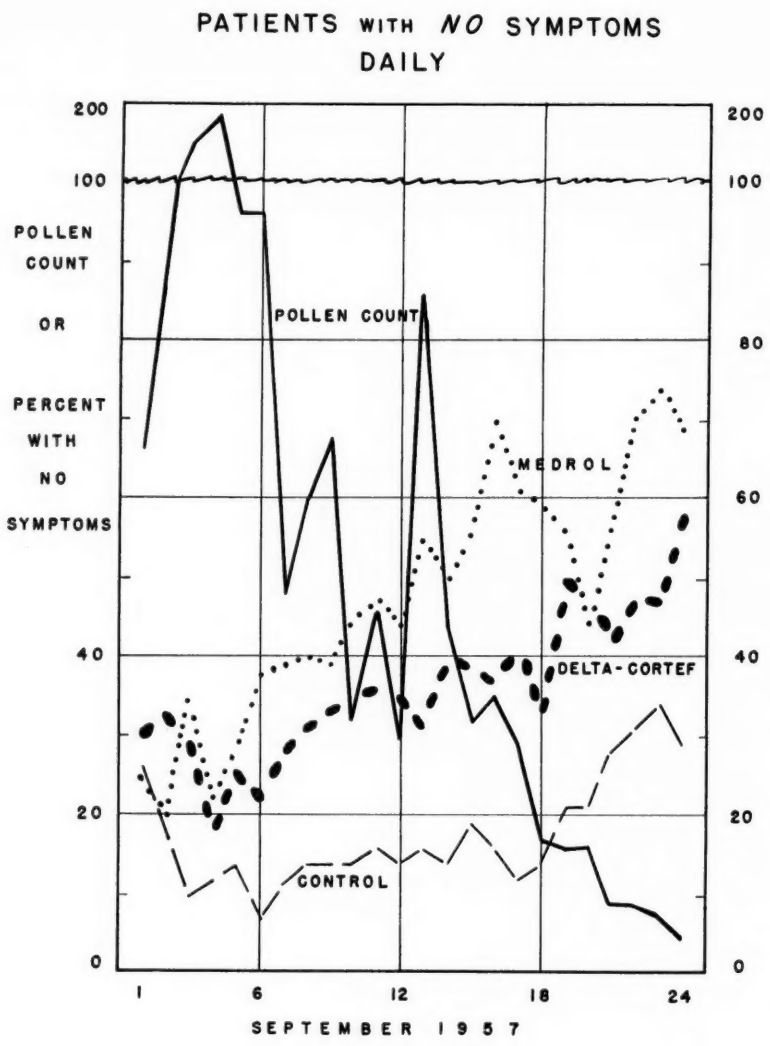


Fig. 3.

three tablets per day, not all followed these orders. Some vials returned indicated that some patients had taken only one to two tablets per day. When questioned about this, they all said that on some days less than three per day gave them adequate relief. The number of tablets left in the vial was, therefore, another means of comparing the efficacy of the two steroids. Of the 2,568 prednisolone tablets given to 856 patients from August 14 to September

30, there were seventy-three (2.8 per cent) left. Of the 2,544 methylprednisolone tablets given to 848 patients, ninety-five (3.7 per cent) remained. This was further evidence of the increased effectiveness of methylprednisolone.

Side Reactions.—Sixteen of the forty-four patients on prednisolone had a total of twenty-two side reactions, while eleven of forty-two patients on methylprednisolone suffered a total of only thirteen side reactions. Table I lists the side reactions suffered by all patients. Patients on prednisolone had about 30 per cent more side reactions than those on methylprednisolone. No patient had to discontinue either medication because of side reactions.

TABLE I. SIDE REACTIONS

TYPE OF SIDE REACTION	PREDNISOLONE	METHYLPREDNISOLONE
Total number of side reactions	22	13
Patients with side reactions	16	11
Insomnia	2	2
Headache or perspiration	4	3
Palpitation	1	—
Fatigue	3	2
Flatulence	1	—
Dizziness or nausea	1	1
Abdominal cramps	1	1
Epigastric distress or heartburn	2	—
Increase of appetite	3	—
Urinary frequency	1	1
Nocturia	3	1
Acneform eruption	—	2

COMMENT

Feinberg and colleagues[6] found that, milligram for milligram, methylprednisolone was equal to or slightly more potent than prednisolone. Our findings confirm this observation. In our hands, however, methylprednisolone appeared to be less toxic than prednisolone. The effectiveness of any medication is measured not only by its potency but also by its tolerance. On both counts, methylprednisolone has some advantages. It is a worthy addition to the corticosteroid group.

SUMMARY AND CONCLUSIONS

1. One hundred thirty-one patients were divided into three groups—forty-four on prednisolone, forty-two on methylprednisolone, and forty-five on no steroids—for study during the 1957 ragweed hay fever season.

2. Methylprednisolone was shown to be slightly more potent than prednisolone in all patients studied.

3. Methylprednisolone was shown to have fewer side reactions than prednisolone in all patients studied.

4. A daily dosage of 15 mg. of either drug was inadequate to control symptoms satisfactorily when the pollen count was at its highest.

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THE ROLE OF ADRENOCORTICAL STEROIDS IN THE TREATMENT OF INTRACTABLE BRONCHIAL ASTHMA

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INTRODUCTION

THE adrenocortical steroids have been used by numerous investigators in the treatment of various allergic disorders over a period of years. Physicians now agree that these compounds are effective in suppressing symptoms but that they do not "cure" any allergic disease. It has been convincingly demonstrated that cortisone and the newer steroids, because of their relatively slow therapeutic benefit are of little use in the treatment of shocklike reactions which occasionally occur in certain persons after a bee sting or following injection of an antitoxin. Since these agents effect only a suppression of symptoms and since their long-continued use may lead to peril, it behooves all physicians to employ more conservative therapy initially and to correct underlying allergic conditions promptly prior to resorting to prolonged maintenance with steroids.

Asthma may be divided simply into two main categories: asthma with an allergic basis and asthma of undetermined etiology. In the nonallergic group descriptive terms, such as intrinsic, infectious, psychologic, or nervous, have been added with some justification, but definite proof of etiology is lacking. In a few of these patients with asthma of unknown etiology, the disease cannot be controlled successfully by diverse methodologies. Some of these unfortunate persons have tried many doctors, numerous climates, and several forms of witchcraft to no avail. Gradually they become invalids in all spheres of life. Indeed, asthma may even threaten their limited existence. Such patients may be candidates for daily maintenance therapy.

The purpose of this article is to discuss experiences with continued adrenocortical steroids in a group of patients with severe, intractable asthma of undetermined etiology.

METHODS

In early 1951 ten patients with severe, intractable asthma of unknown etiology were given enough cortisone for complete suppression of their symptoms. At intervals of five days the daily dose was lowered until symtoms

From the Medical Services of the Massachusetts General Hospital.

Supported by grants from the Upjohn Company and funds from the Allergy Clinic Fund. Cortisone, hydrocortisone, prednisone, and prednisolone have been generously supplied by the Upjohn Company, Merck and Company, Inc., and The Schering Corporation.

Received for publication Jan. 28, 1958.

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reappeared. As hydrocortisone, prednisone, and prednisolone became available, studies of similar groups were started. Certain patients were placed serially on each of these four compounds. Since asthma of even this nature may disappear spontaneously, each patient was removed from steroids at approximately yearly intervals to ascertain whether such therapy was still indicated. Throughout the study, each patient was seen at regular two-week intervals for physical examination and laboratory tests. Medical care was made available twenty-four hours a day; all abnormalities were reported promptly, and as complications or problems arose these were promptly studied and treated as required.

OBSERVATIONS

Selection of Patients.—It is unwise to select a patient for prolonged steroid therapy unless a detailed past history and recent observation indicate that intensive routine treatment has proved inadequate to control symptoms. To evaluate such patients, hospitalization is recommended. Many of these patients will respond to hospital care and conservative medication. In the event that definite improvement does not occur, treatment with cortisone or similar agents may be decided upon as a calculated risk.

PRINCIPLES OF DOSAGE

Enough of the selected adrenocortical steroid must be given initially to free the patient completely of his symptoms. The daily dose is then gradually reduced until the lowest possible daily dose—namely, the one which is just adequate to keep the patient free of symptoms—is determined. Establishment of such end points with different steroids can be used to advantage in comparing various adrenocortical steroids as to optimum dosage.

All of the patients listed in Table I had severe, intractable asthma of unknown etiology and of long duration. When cortisone or hydrocortisone was chosen, 300 mg. was given during the first twenty-four hours, and then 200 mg. was given daily until each patient was subjectively and objectively free of asthma. With prednisone or prednisolone, 200 mg. was sufficient for the first day. The initial day's therapy was followed by 100 mg. every twenty-four hours until no symptoms were present. Table I lists the total clearing dose for each patient. Several patients have clearing doses recorded for more than one compound. This occurred when one steroid had been discontinued, only to be replaced by another after symptoms had become severe again. Table I shows that cortisone, hydrocortisone, prednisone, and prednisolone are all capable of freeing a patient of asthmatic symptoms. No one preparation is demonstrated as having any advantage over the other three. The total clearing dose is obviously individual for each patient and does not depend upon severity of asthma.

In Fig. 1 the number of patients clearing on each day of therapy (three to twenty-one days) is shown for cortisone, hydrocortisone, prednisone, and prednisolone. It will be observed that the variation is great for each agent. Again, no compound proved its superiority.

TABLE I. TOTAL CLEARING DOSE

PATIENT	SEX	AGE	CORTISONE (MG.)	HYDROCORTISONE (MG.)	PREDNISONE (MG.)	PREDNISOLONE (MG.)
M. A.	F	44	850			
A. B.	F	60	650			
B. B.	F	54	1,474			
B. Bl.	F	52		3,940		
P. B.	M	73	825			
B. C.	F	47	2,300			
E. C.	F	57	1,475			
J. C.	F	66	1,250	1,400		
A. D.	F	61				
M. D.	F	57	725			170
C. E.	M	55		1,150		
J. E.	M	46		1,700		
T. F.	M	68 ('57)	800			
D. G.	F	30	1,000			
J. G.	M	60	1,200			
M. G.	F	62			440	
T. G.	M	34	775			
W. G.	M	61	1,900			
E. H.	F	59		1,100		
F. H.	M	65	1,200			
E. Kos.	F	44	750			
E. Koz.	F	48	3,125			
G. K.	M	70				
E. L.	M	39	1,200		715	
E. McF.	M	51	1,350			
A. M.	F	51		460		
E. M.	F	48	1,500		200	
G. M.	M	46			800	
E. M.	F	39	625		2,335	
D. M.	M	61	950			
M. M.	F	62	1,816			
G. Mc.	M	57		1,000		
M. O'K.	F	60	2,700			
G. O'S.	F	42			825	
D. P.	M	48	1,375		610	
E. P.	F	57		3,800		
H. P.	M	56	1,150	2,000	625	
J. P.	F	43	1,375	3,940		
M. P.	F	62				
P. P.	M	42	1,420	1,950		
A. R.	M	50				
C. R.	F	54			475	
C. R.	M	60	500			810
E. R.	F	57				
M. R.	F	64	2,100		400	
C. S.	M	50				
F. S.	F	47	1,325	2,500		
H. S.	F	34				
L. S.	F	43	1,325	1,050		
J. S.	M	47	1,850			
M. S.	F	34	800			
L. T.	F	20	600			
A. W.	F	59	1,150			
E. W.	M	64	875			
G. W.	F	74		675		
L. W.	F	65	1,200			
M. W.	M	57	1,100			
R. W.	M	49	800			
S. W.	F	48		1,510		
N. Z.	F	56	2,525			

Table II lists the average daily maintenance dose (in milligrams required every twenty-four hours to keep a patient free from symptoms). A dose is listed for each adrenocortical steroid on which each patient has been maintained. Again patients vary greatly. It is obvious that, milligram for milligram, prednisone and prednisolone are more potent than cortisone or hydrocortisone. The difference, however, varies from patient to patient. For

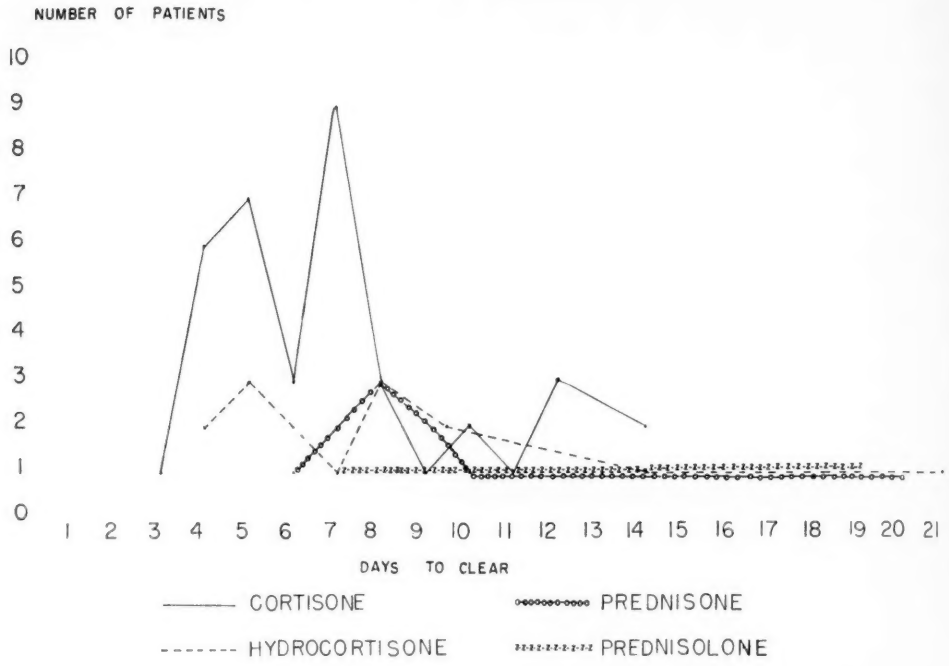

Fig. 1.

example, Patient M. D., a 57-year-old woman, requires 65 mg. of cortisone and only 10 mg. of prednisone every twenty-four hours. The ratio is 6.5 to 1, whereas Patient C. S., a 50-year-old man, needs 140 mg. of hydrocortisone to 100 mg. of prednisone (a ratio 1.4 to 1). Table II suggests that the ratio of cortisone or hydrocortisone to prednisone or prednisolone is not 5 to 1, as advertised, but closer to 3 to 1 in the control of bronchial asthma.

DESTINY OF PATIENTS

The best fortune for these patients on long-term adrenocortical steroids would be withdrawal of their medication without reappearance of severe symptoms. At about yearly intervals each has been separated from maintenance therapy. To date only three patients of this group have been removed successfully. Patient M. P., a 62-year-old woman, Patient E. R., a 57-year-old woman, and Patient C. S., a 50-year-old man, have been off steroids for two years. Patients M. P. and E. R. have had no asthma, and Patient C. S. is now

TABLE II. DAILY MAINTENANCE DOSE (IN MILLIGRAMS)

PATIENT	SEX	AGE	CORTISONE	HYDROCORTISONE	PREDNISONE	PREDNISOLONE
M. A.	F	44	59			
A. B.	F	60	50.4			
B. B.	F	54	55			
B. Bl.	F	52		150		
P. B.	M	73	65	49	10	10
B. C.	F	47	100	68		
E. C.	F	57	85			
J. C.	F	66	100	60	15	
A. D.	F	61				7
M. D.	F	57	65	44	10	
C. E.	M	55		50		
J. E.	M	46		72		
T. F.	M	68 ('57)	71			
D. G.	F	30	63			
J. G.	M	60	100		20	
M. G.	F	62			20	
T. G.	M	34	83			
W. G.	M	61	100	100		
E. H.	F	59		54	20	20
F. H.	M	65	75			
E. Kos.	F	44	75			
E. Koz.	F	48	67	50	15	15
G. K.	M	70			20	
E. L.	M	39	125	100	25	25
E. McF.	M	51	81			
G. Mc.	M	57		50		
A. M.	F	51	25		10	10
D. M.	M	61	73	56	20	10
E. M.	F	39	63	43	20	
E. M.	F	48	50		10	10
G. M.	M	46			20	
M. M.	F	62	68			
M. O'K.	F	60	100		20	
G. O'S.	F	42			10	
D. P.	M	48	158	70		
E. P.	F	57		100	26	
H. P.	M	56	100	55	15	
J. P.	F	43	67			
M. P.	F	62		50		
P. P.	M	42	150	120	20	20
A. R.	M	50			15	
C. R.	F	54				20
C. R.	M	60	117	80	40	40
E. R.	F	57			50	
M. R.	F	64	150			
C. S.	M	50		140	100	100
F. S.	F	47	100	80	30	
H. S.	F	34		66		
J. S.	M	47	31			
L. S.	F	43	108		18	
M. S.	F	34	100	100		
L. T.	F	20	100			25
A. W.	F	59	37	31	10	10
G. W.	F	74		80		
E. W.	M	64	75			
L. W.	F	65	72			
M. W.	M	57	75		30	
R. W.	M	49	96			
S. W.	F	48		38		
N. Z.	F	56	77		15	

able to control mild symptoms with epinephrine, ephedrine, and aminophylline. It appears likely that asthma in these patients disappeared independently of their steroid medication and that it was fortuitous that each was removed at the appropriate time. Incidentally, all three of these patients presented acute withdrawal symptoms of nausea, vomiting, severe headache, and muscular and joint pains. This syndrome[1] is one that has previously been described with discontinuation of long-term steroid therapy. Muscular weakness, stiffness of joints, and easy tiring persisted in all three for six months, but now all are free of any withdrawal symptoms.

Three patients have died. The case of Patient W. G., a 61-year-old man on cortisone, was reported in detail in an earlier publication.[2] Post-mortem findings included pneumonia, and it appears fair to consider steroid therapy as a factor in his death. Patient T. F., a 68-year-old man, on cortisone, died of bronchiogenic carcinoma, and Patient G. W., a 74-year-old woman, while on hydrocortisone, died quietly in her sleep at home (no autopsy). In these last two patients it would be difficult to ascribe any role in regard to death to the steroids.

TABLE III

DISEASES WHILE ON STEROID THERAPY	NUMBER OF PATIENTS	ADRENOCORTICAL STEROID AT TIME
Compressed vertebral fractures	3	Cortisone or hydrocortisone
Gastrointestinal bleeding, cause undetermined	2	Hydrocortisone
Duodenal ulcer	1	Prednisone
Duodenal ulcer with hemorrhage	1	Cortisone
Pneumonia	2	Cortisone
Ruptured intervertebral disc	1	Prednisone
Thrombophlebitis	4	Prednisone or prednisolone
Pulmonary infarct	4	Prednisone or prednisolone
Extensive cellulitis	3	Hydrocortisone or prednisone
Fractured patella	1	Prednisone
Hyperglycemia and hyperglycuria with extensive cellulitis	2	Prednisone
Benign hypertrophy of prostate	2	Prednisone
Prostatitis and cystitis	1	Prednisone
Myocardial infarct	2	Hydrocortisone or cortisone
Cerebral vascular accident	1	Off at time
Muscular back strain	2	Prednisone
Herpes zoster	1	Prednisone
Senile psychosis	1	Hydrocortisone
Purpura (easy skin bruising)	23	All four compounds

Table III lists twenty different serious disorders noted in this group of patients. The problem of osteoporosis and compressed vertebral fractures[2-4] was discussed previously. The three cases of compressed vertebral fractures in this group all appeared at about the same date. This led to giving most male patients 400 mg. of testosterone cyclopentylpropionate intramuscularly at weekly intervals and women beyond the menopause Premarin in cycles of

10 mg. daily for twenty-eight days with the next ten days off. Since the adoption of this regime, no further cases of vertebral fractures have appeared, but twenty-four-hour determinations of calcium excretion in the urine to date have indicated that androgenic and estrogenic therapy has only diminished, but not stopped, excessive excretion of calcium in the urine. Excessive urinary excretion of calcium does not always occur in these patients. For example, Patient C. R., a man aged 60 years, has always received large daily doses of steroids without androgenic therapy, and his twenty-four-hour urinary excretion of calcium has never reached 100 mg. Roentgenograms of his thoracic and lumbar vertebrae, moreover, show no osteoporosis after six years of continuous therapy.

In the past seven years, three patients have developed gastrointestinal bleeding while on steroids. A duodenal ulcer was found in one patient so bleeding, and surgery was required for control. In the two others no bleeding point was demonstrated, and a medical regime proved sufficient. In none of these patients was steroid therapy interrupted.

With extensive cellulitis, two patients developed temporary hyperglycemia and hyperglycuria. In neither case was prednisone stopped, and in both patients the glucose tolerance curve was normal, once the cellulitis was checked.

Patient C. R., a 60-year-old man, developed a severe infection of the tendons of his right wrist. The surgical service decided that prednisone should be discontinued to enable them to deal more adequately with his infection. Withdrawal symptoms were severe, and during this time the patient suffered a cerebral vascular accident which left him with a residual right temporal hemianopsia and slight dysarthria. His condition remained unsatisfactory until prednisone was resumed.

Purpura (easy bruising of skin) has been noted in twenty-three patients, but its cause is not clear. When a patient is removed from steroids, this purpura clears.

Other disorders encountered by these patients include fractured patella, thrombophlebitis, benign hypertrophy of prostate, prostatitis, cystitis, myocardial infarct, pulmonary infarct, muscular back strain, herpes zoster, and senile psychosis. The role of concomitant steroid therapy in patients with these disorders is not clear but certainly deserves serious consideration.

Most of these patients display some degree of hyperadrenalism, such as moon face, abnormal distribution of weight with increased fat in abdominal, facial, supraclavicular, and lower cervical areas, hirsutism in females, and facial rubor. Others have developed temporary increases in both the systolic and diastolic components of their blood pressure.

A check of freedom from possible complications fails to favor either cortisone, hydrocortisone, prednisone, or prednisolone. All these patients have been maintained on a diet variously restricted in calories and limited to 500 to 1,000 mg. of sodium daily. Excess weight occurs if patients eat at will, for all four compounds are accompanied by an increase in appetite. With regard to clinical edema, even prednisone and prednisolone given for a long period of time will cause fluid to accumulate unless dietary restriction of salt is practiced.

DISCUSSION

This study clearly indicates that cortisone, hydrocortisone, prednisone, and prednisolone are useful in controlling the symptoms of asthma and that it is possible to suppress symptoms with these agents for as long as seven years. In fact, the adrenocortical steroids are the most effective compounds in relieving the asthmatic patient of his symptoms. Their marked effectiveness led to great initial enthusiasm which cooled somewhat when it became obvious that their use over a period of time could result in most unpleasant side reactions. Steroid chemists have worked to develop different compounds which would be as effective as cortisone but would not result in undesirable side reactions. Obviously hydrocortisone, prednisone, and prednisolone have not proved their superiority. The search for efficient steroids free of unpleasant reactions continues. Indeed, there are now new agents on the market. Only long-continued use of these newer agents over a period of years will determine their true status in the treatment of severe, intractable asthma of unknown etiology.

Many investigators and physicians hoped that the adrenocortical hormones would lead to a better understanding of the etiology of asthma. To date this wish has not been fulfilled. The exact mechanism of the relief of asthmatic symptoms by cortisone and related compounds is not understood, and those with asthma of unknown etiology still must depend on drugs which afford only symptomatic relief.

Results to date indicate that long-term maintenance adrenocortical steroid therapy should be limited to patients with long-standing severe asthma of undetermined etiology. Decision for such therapy depends on a careful evaluation and study of each patient. A hasty decision may well be regretted by both patient and physician. No general rules are applicable, but patients with roentgenographic evidence of vertebral osteoporosis are poor risks, as are women whose ovaries and uterus have been surgically removed. Patients with duodenal ulcers or tuberculosis must assume even more risks. There is the suggestion that those with chronic thrombophlebitis and vascular disorders must be considered more vulnerable. Once the patient is on maintenance cortisone or like substances, it is essential that he be under medical supervision and remain on a low-sodium diet throughout the course of therapy, even if his maintenance drug is prednisone or prednisolone.

CONCLUSIONS

1. Cortisone, hydrocortisone, prednisone, or prednisolone will control the symptoms of severe bronchial asthma of unknown etiology for years, provided that the proper clearing dose and the correct daily amount are given. The proper clearing dose must be adequate for complete clearance of symptoms, and the correct daily dose is the least amount that will just suppress symptoms.

2. The use of all four compounds has been accompanied by the effects of hyperadrenalism, and serious illnesses have occurred with all four.

3. Cortisone is the cheapest drug to use and it is probably the agent of choice, because this study suggests that no one compound has any consistent therapeutic advantage over the others in long-continued therapy.

4. Patients with serious asthma may benefit from control of symptoms with long-term daily administration of one of the adrenocortical steroids, but they must assume certain definite risks.

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PREDNISOLONE ALONE AND IN COMBINATION WITH HYDROXYZINE

A Comparative Study in Allergic Disorders

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THE effectiveness of the corticosteroids in the relief of various allergic manifestations has already been well documented. Continued investigations with newer corticosteroids have opened a wide area for study. In the past few years the metisteroids, delta analogues of cortisone and hydrocortisone, have been used more frequently because they have less sodium-retention properties and are equally effective.[1] Unfortunately, all of these corticosteroids, if used in large dosage, can produce the hyperphysiologic effects of moon facies, edema, and other reactions which are all well recognized. One of the less common side effects of these compounds is insomnia. In view of this, and also because of the psychosomatic factors in allergy, a comparative study of prednisolone alone and prednisolone combined with a tranquilizer, hydroxyzine (Atarax), was undertaken.

METHODS AND MATERIALS

At first, a "double blind" study was started. In view of many practical difficulties, however, such as concurrent infections and sudden withdrawal of steroid, this method was soon substituted for a "single blind" survey.

Eight different sets of medication were available in tablets of the same size, color, and taste. These tablets consisted of prednisolone in doses of 5.0, 2.5, and 1.0 mg. alone; a combination of each of these dosages with 10 mg. of Atarax; 10 mg. of Atarax alone; and a placebo. The ingredients of these tablets were known only to the physician. The patient was given just enough medication to last until his next weekly visit.

Fifty-eight patients (thirty-one females and twenty-seven males) from private practice and the Allergy Clinic at the Buffalo General Hospital were finally available for comparative analysis. They varied in age from a 14-month-old infant with infantile eczema to a 77-year-old chronic asthmatic. Many of these patients had more than one allergic disorder. Each patient was given a symptom card and advised to record the number of hours of freedom from symptoms each day, as well as the amount of supplementary medication, such as bronchodilators, etc., that was necessary to keep him comfortable. This card was reviewed, the patient was examined, and weight and blood pressure were

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Material (Ataraxoid) furnished and this study supported, in part, by a grant from Chas. Pfizer & Co., Inc., Brooklyn, New York.

Received for publication Feb. 20, 1958.

noted each week by the attending physician. The dosage of the prednisolone was gradually reduced each week, if the patient was well, until a definite maintenance dosage was established. Then, depending upon what combination the patient had been on, the tranquilizer was either added or withdrawn. As was described earlier, at first, each dose of prednisolone contained either 10 mg. of hydroxyzine or none at all. As our studies continued, however, in many instances, we tried 5.0 mg. of Atarax per dose of steroid, or even up to 20 or 30 mg. of the tranquilizer per dose. These variables, however, were not attempted until after the maintenance level of the metisteroid had previously been determined.

TABLE I. DURATION OF STEROID THERAPY*

YEARS	NUMBER OF PATIENTS
Up to 1	21
1-2	16
2-3	12
3-5	3
Over 5	6

*Including previous steroid therapy and our present comparative study.

Fortunately, most of these patients had been on other steroids for long periods of time and their maintenance dosage of prednisolone and/or prednisone had previously been determined. The length of time that patients had been on steroids prior to and including this study is summarized in Table I. Forty-three of the fifty-eight patients studied were under this particular survey for at least four months, and twenty of these for over one year (Table II).

TABLE II. DURATION OF COMPARATIVE STUDY*

MONTHS	NUMBER OF PATIENTS
Under 1	3
1-3	12
4-6	12
7-10	11
11-14	16
Over 14	4

*Comparing prednisolone alone and in combination with hydroxyzine.

RESULTS

The results reported are based on the patients' symptom cards, the subjective complaints, and objective findings observed each week. An evaluation of this type leaves much to be desired with such a small series of patients. In only two patients was the Atarax alone sufficient to control symptoms. They, of course, were not included in the report!

One of these patients, with a pronounced emotional component, experienced complete relief of her "asthma" on 40 mg. of hydroxyzine daily. Another patient, a 25-year-old man with severe chronic giant urticaria for six months, obtained freedom of all lesions on 20 mg. of hydroxyzine four times daily.

Previous treatment with steroids alone, chlorpromazine, meprobamate, and various antihistaminics, as well as thorough elimination diets, environmental changes, and searches for focus of infection, etc., had failed to benefit this man.

Table III illustrates the results of our study. Of the forty-nine patients with bronchial asthma, thirty-three experienced no difference with or without the addition of the tranquilizer (regardless of dosage). Two of this group could not tolerate the hydroxyzine because of drowsiness, but fourteen claimed that they felt better with the addition of Atarax. Three of these patients were as well on a slightly lower dosage of steroid when it was combined with hydroxyzine.

TABLE III. RESULTS OF STUDY

CONDITION TREATED	NUMBER OF PATIENTS	BETTER		SAME
		WITH* ATARAX	WITHOUT† ATARAX	
Bronchial asthma	49	14	2	33
Nasal polyps	9	4		5
Atopic eczema	9	4		5
Chronic urticaria	2	1		1

*Prednisolone plus hydroxyzine (Atarax).
†Prednisolone alone.

Thirty patients had been on steroids for more than eighteen months. Of these, seven were better with the combination, two were worse, and in the remainder the results were the same with or without the tranquilizer. Four of the nine patients with nasal polyps and four of nine patients with atopic eczema reported better results with the combination. It must be remembered, however, that there is duplication here, as several of these patients are listed under more than one allergic condition. A total of nineteen patients (32.7 per cent) seemed better when Atarax was incorporated with the steroid. The reasons for this increased benefit are indicated in Table IV. Four patients had marked pruritus from the steroid alone, but when prednisolone was given in combination with the tranquilizer they had no further itching and could tolerate the prednisolone. It is interesting to note that these same patients had itching from other steroids such as Medrol and 9 alpha—fluoro prednisolone (Kenacort or Aristocort).

TABLE IV. ADVANTAGES OF PREDNISOLONE-HYDROXYZINE

ADVANTAGE	NUMBER OF PATIENTS
Relief of tension	12
Less pruritus	4
Less insomnia	3

The antihistaminics and/or ephedrine, when added to the steroid alone in the patients who developed pruritus, did not relieve the itching, whereas the combination with hydroxyzine (Atarax) was beneficial.

Three other patients were relieved of their insomnia by the combination. All of the remaining twelve patients benefited were very tense, emotionally unstable persons with a strong psychogenic component.

TABLE V. AVERAGE DAILY MAINTANENCE DOSAGE

DOSAGE/MG. RANGE	NUMBER OF PATIENTS	
1-5	8	
7.5	24	44
10	12	
15	9	
20	3	14
Over 20	2	

The average daily maintenance dosage of the patients studied is shown in Table V. Forty-four of the fifty-eight patients studied were kept comfortable on 10 mg. or less of either prednisolone alone or in combination with Atarax. Three of the fourteen patients requiring over 10 mg. daily were able to get along on a smaller dosage of corticosteroid when it was combined with the tranquilizer. Also, ten of these fourteen patients who required larger dosages of steroids had been on long-term steroid therapy prior to our present study. It has been our practice to give supplemental therapy (bronchodilators, expectorants, etc.) to these patients, thus reducing the required maintenance steroid dosage to a minimum. If steroids only were used, the maintenance dosage naturally would be much higher.

TABLE VI. SIDE EFFECTS

TYPES OF SIDE EFFECTS	NUMBER OF PATIENTS
Weight gain (over 3 pounds)	18
Moon facies	7
Pruritus	5
Drowsiness	4
Miscellaneous	7
Total number of patients studied: 58	
Total number of patients with side effects:	31 (41 side effects)

The side effects encountered were similar to those previously reported for prednisolone and prednisone (Table VI). Thirty-one of our fifty-eight patients had forty-one different hyperphysiologic effects. Frank edema was noticeably lacking, although eighteen patients gained more than three pounds in weight during the course of this survey. However, much of this could be attributed to the fact that the patients were feeling better and, hence, had an increased appetite. Nevertheless, six patients gained ten or more pounds. Moon facies was definitely present in seven of our subjects, and two women developed "buffalo humps." Generalized pruritus of the skin was reported by five patients. Four of these five patients were able to tolerate the combination of steroid and tranquilizer without itching. However, an additional four patients could not take the combination tablet because of the drowiness produced. Other side effects noted were an elevation in blood pressure and albuminuria in a woman who had been on steroids for more than five years. Another complained of cramps in the legs; a few had insomnia, which was corrected when the combination therapy was prescribed; two others had bloating and heart burn; and one boy had enuresis and frequency of urination.

EFFECTS OF CONTINUOUS LONG-TERM STEROID THERAPY

Six patients in our study had been on corticosteroids continuously for more than five years. The duration of therapy and ill effects are listed in Table VII. As mentioned previously, one woman developed hypertension, albuminuria, and a moon facies. Whether this would have occurred in the natural course of events in a 57-year-old woman who was not receiving steroids is difficult to ascertain. Weight gain and moon facies were also noted. It was not possible to take these patients off their steroids or to lower their maintenance dosage for more than twenty-four hours without a recurrence of symptoms. On their maintenance level, however, which was under 10 mg. of metisteroid in all instances except for the case of hypertension, the patients could lead useful and comfortable lives. There has been no evidence of osteoporosis in these patients.

TABLE VII. LONG-TERM STEROID THERAPY

PATIENT	AGE	DURATION (MONTHS)	SIDE EFFECTS
L. H.	58	62	Gained 15 lbs.
B. K.	45	66	None
G. L.	59	80	Gained 11 lbs.
J. M.	57	67	Hypertension, albuminuria, moon facies
E. S.	69	82	Gained 5 lbs.
M. F.	?	76	Moon facies

PEDIATRIC SECTION

Twelve of the patients used in this study were under 20 years of age. There were six with atopic eczema or infantile eczema, three with allergic rhinitis, and nine with bronchial asthma, either alone or in combination. Four of the six patients with atopic eczema were better on the combination tablet, as were four of the nine patients with bronchial asthma. The side effects were essentially as described for the entire group, and only one child needed more than 10 mg. daily to keep him comfortable. Three children had less itchy skin and one had less insomnia when taking the steroid with the tranquilizer.

DISCUSSION

Although the evaluation of a comparative study based primarily on subjective reports leaves much to be desired, we tried to circumvent these objections by means of a "single-blind" study, plus symptom cards, close observations, and objective examinations. Recently, Koteen[2] reported the results of a "double-blind" study of a tranquilizing agent. He noted that meprobamate in the usual dosage prescribed had no greater effect in relieving symptoms than did the placebo in twenty-five unselected patients with emotional tension and/or muscle discomfort.

Although Warteur[3] reported that the effect of prednisolone on rheumatoid arthritis is enhanced by hydroxyzine in many instances, permitting a substantial reduction in the dosage of steroid, this was not our experience with allergic patients. Only three patients of our group were able to have a reduced amount of steroid by the addition of hydroxyzine, despite the fact that in several instances the hydroxyzine dosage was increased to as much as 80 or 120 mg. daily.

Recently, Brown and Seideman[4] reported that prednisolone with hydroxyzine was significantly more effective than prednisolone or hydroxyzine given separately. These investigators, however, gave each of their patients 20 mg. of prednisolone daily and did not find a minimal maintenance dosage. Their patients were observed for only two-week periods on each of the various combinations. In our present study the findings reported were obtained from longer periods of observation and many trials with the different combinations of steroid and tranquilizer in each patent.

However, definite benefit was obtained in nineteen of these patients when the combined therapy of prednisolone and hydroxyzine was prescribed. The chief factors were relief of tension, pruritus, and insomnia.

The emotional factors in allergy are well recognized, but the solution to this aspect should not be limited to the use of tranquilizers. It is most important to try to understand these patients' problems. This can best be accomplished at the time of the weekly visits, when the patient is given reassurance and encouragement and allowed to have a close patient-physician relationship. This is psychotherapy at a very superficial level. For the great majority of patients, therefore, the addition of a tranquilizer to steroid therapy is neither necessary nor beneficial. At the Southwestern Allergy Forum in May, 1957, Johnson and Cazort[5] reported similar findings.

All patients in this study obtained relief of symptoms if given sufficient amounts of prednisolone. Naturally, the higher the dosage given, the more likely one would be to encounter side effects, such as moon facies, weight gain, etc.

CONCLUSIONS

1. Nineteen of the fifty-eight patients studied responded more favorably with prednisolone plus hydroxyzine than with prednisolone alone. However, the dosage of steroid could be lowered in only three instances when the tranquilizer was used in combination with the steroid.

2. Six patients have been on steroid therapy for more than five years without any demonstrable ill effects (except in one case).

3. For those patients who need a tranquilizing agent in addition to the steroid, the tranquilizer should be prescribed separately and the dosage of each material adjusted for the individual need and responses of the patient.

4. The majority of allergic persons seen in private and clinic practice did not benefit by the addition of a tranquilizer to maintenance dosage of corticosteroids.

5. A tranquilizer was of benefit in allaying the insomnia and itching secondary to corticosteroids and in relieving the tensions of some of the patients with chronic allergic disorders.

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THE INCIDENCE OF SUBSEQUENT RAGWEED POLLINOSIS IN SYMPTOM-FREE PERSONS HAVING POSITIVE REACTIONS TO RAGWEED POLLEN EXTRACT

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INTRODUCTION

IN THE course of complete skin testing of allergic patients of all ages, it has been our custom for many years to include ragweed pollen regardless of the allergic condition and age of the patient. It was felt that eventually the information so obtained might shed some light upon the natural history of the development of ragweed pollinosis. The purpose of this article is to report on patients so tested with respect to those who gave positive cutaneous reactions to ragweed pollen but who did not suffer from pollinosis of any kind (tree, grass, or weed) at the time of the tests. The particular problem was whether or not a positive reaction in such cases had any prognostic value. This would test the truth of the general assumption by most allergists that such a finding indicates that in all probability the patient will eventually develop ragweed pollinosis. This study shows the results obtained after such patients were actually followed for a number of years. The implication of this is that if a significant number of these patients were later to develop pollinosis the practice of giving injections of ragweed or other pollen as a prophylactic measure when the patient receives other injections, such as house dust, would be justified.

METHOD

Since 1931 every patient who had been skin-tested because of a known or suspected allergy and who had given a positive skin test reaction to ragweed pollen, but who did not have clinical ragweed pollinosis, was recorded. In May, 1957, a follow-up study of those patients was started. Fifty-six patients were contacted by telephone. In some cases, the patient's wife or mother (if the patient were still a child) was interviewed instead of the patient, but in all such cases only those wives or mothers living in the same house as the patient were consulted. Twelve of the total of sixty-eight patients were questioned by mail. Each patient was asked if he had developed rose fever (grass pollinosis) or hay fever (ragweed pollinosis), and the symptoms were described to the

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Presented at the meeting of the American Academy of Allergy, Philadelphia, Pennsylvania, Feb. 3, 1958.

Received for publication Nov. 25, 1957.

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patient. These symptoms are, in lay terms, itching, red, swollen eyes; running, obstructed, itching nose; sneezing; or wheezing. Any or all of these symptoms were accepted as diagnostic if they occurred seasonally and only during the time of ragweed pollination (August 15 to October 1).

Other information was obtained from the original charts. Skin test reactions were considered only if they were 2 plus by scratch test or 3 plus by intradermal test. Age was recorded as of the date of the skin test, and sex was also noted. The original diagnosis has not been considered for correlation, since all the patients had some allergic disease (many patients had more than one) but none had ragweed pollinosis. Furthermore, these diseases were not regarded as essential for the purpose of the current study. In short, the valid information being reported is the age, the sex, the cutaneous reaction to ragweed pollen, and the ultimate development or nondevelopment of ragweed pollinosis.

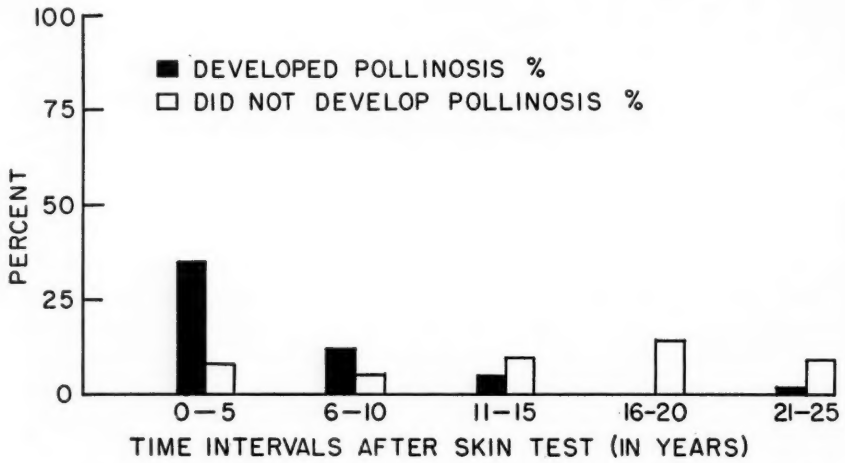

Fig. 1.—This graph shows the ultimate outcome for all age groups totaled. The vertical height of each column represents per cent of all the sixty-eight patients studied, and the columns are grouped at various time intervals after skin testing. See text for discussion.

RESULTS AND DISCUSSION

A total of 167 patients have been studied since 1931. During this time approximately 10,000 allergic persons have been seen in this office. Thus, about 1.7 per cent of all our allergic patients had positive skin test reactions to ragweed pollen but did not suffer from ragweed pollinosis. Of the 167 patients recorded, ninety-nine were unacceptable for this series (1) because they had less than the specified value for skin tests (2+ scratch or 3+ intradermal); (2) because they had received prophylactic pollen injections in the interim (no patients in this series received any pollen injections prior to the development of ragweed pollinosis); or (3) because of error in the original diagnosis of absence of pollinosis, discovered when the patients were queried later. Thirty-one patients had moved out of town and were requested by letter to answer

the same questions that the others were asked on the telephone. Nine letters were returned as undeliverable, thus, only about one-third of the mail contacts failed to respond. The sixty-eight patients reported here include twelve who answered by letter and fifty-six who answered directly by telephone.

The general trend of outcome for these patients can be seen in Table I. Of the group as a whole, 53 per cent of the patients developed ragweed pollinosis and 47 per cent did not.

TABLE I

AGE WHEN SKIN-TESTED (YEARS)	TIME INTERVAL (YEARS) PATIENTS FOLLOWED AFTER SKIN TESTS										TOTAL PATIENTS IN AGE GROUP
	0-5		6-10		11-15		16-20		21-25		
	A	B	A	B	A	B	A	B	A	B	
0-5	14	2	4	1	1	2	0	1	0	1	26
6-10	3	2	2	1	0	1	0	1	1	2	13
11-15	3	1	2	0	2	0	0	3	0	1	12
16-20	1	0	0	0	0	1	0	2	0	2	6
21-40	2	0	1	1	0	2	0	0	0	2	8
41-57	0	0	0	0	0	1	0	2	0	0	3
Totals	23	5	9	3	3	7	0	9	1	8	68

A = Number of patients in any age group who developed pollinosis at a given time interval after the skin test was done.

B = Number of patients in the same age group who did not develop pollinosis in that same interval. For example, of twenty-six patients tested between the ages of 0 and 5 years, there were sixteen who were followed up to a 5-year period; of these, fourteen developed pollinosis and two did not; of five patients followed for six to ten years, inclusive, four developed pollinosis and one did not, etc.

This table is illustrated graphically in the figures that follow.

Of the thirty-six patients who developed symptoms, 88 per cent did so within ten years after testing and 64 per cent did so five years after testing. In other words, regardless of the age at the time of skin testing, if pollinosis does not develop within ten years it probably will not develop at all.

Another fact of interest is revealed in Figs. 2 to 7 and summarized in Fig. 8, *A* and *B*.

It can be seen that as the age at which the skin tests were first performed advances, fewer patients will ultimately develop pollinosis. That is, of the seventeen patients aged 16 years and over, only four (25 per cent of all patients over 16 years of age) developed pollinosis at any time interval after testing, as compared to a total of thirty-two patients less than 16 years of age (63 per cent of all patients under 16 years of age) who developed pollinosis. Of those four patients over 16 years of age who did develop pollinosis, the majority developed it in the first ten years, just as patients in the other age groups did.

Finally, another fact of importance is that most of the patients who do not develop pollinosis are concentrated in the older age groups. This is a corollary of the facts noted previously. A total of thirteen patients 16 years of age and over (70 per cent of all patients over 16) did not develop pollinosis, as compared to a total of nineteen patients (35 per cent of all patients under 16 years) who did not develop pollinosis.

In summary, it would appear that those patients under 16 years of age at the time of skin testing will develop most of the pollinosis that is developed (63 per cent), whereas most of those over 16 years at the time of skin testing will escape pollinosis (70 per cent).

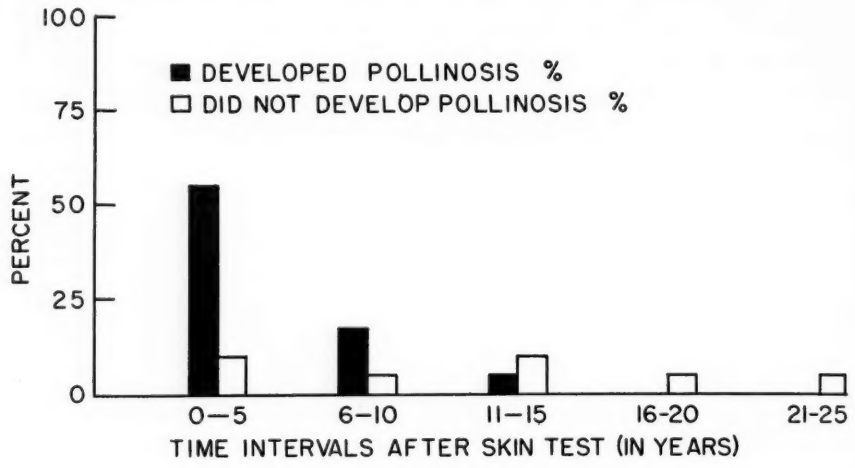

Fig. 2.—Age group 0 to 5 years.

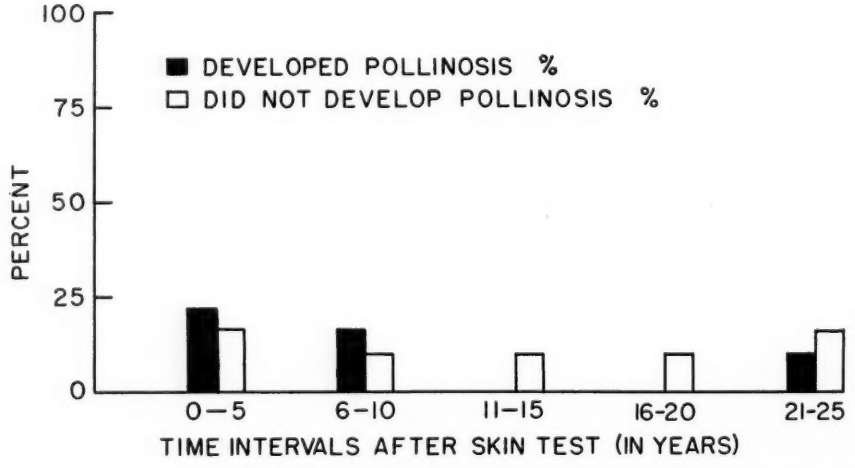

Fig. 3.—Age group 6 to 10 years.

Figs. 2 to 7.—Each drawing shows the ultimate outcome for the particular age group noted, and shows it in per cent of the total number of patients in that age group. The age is taken at the time of skin testing. Each figure shows the outcome for its age group at various time intervals after skin testing. See text for discussion.

Actually, it is not possible to be so positive about the outcome for those patients who failed to develop ragweed pollinosis. Although all patients recorded have been followed up to May, 1957, the length of follow-up varied from less than two years (but more than one year) up to twenty-four years. Thus, these figures are partly influenced by a factor of time—whether the

patients were seen two years ago, ten years ago, or twenty years ago. More useful figures can be obtained from Figs. 2 to 7, which show the ultimate outcome for any age group of patients. These graphs give the whole spread of time, and a better, although incomplete, idea can be gained from them. For

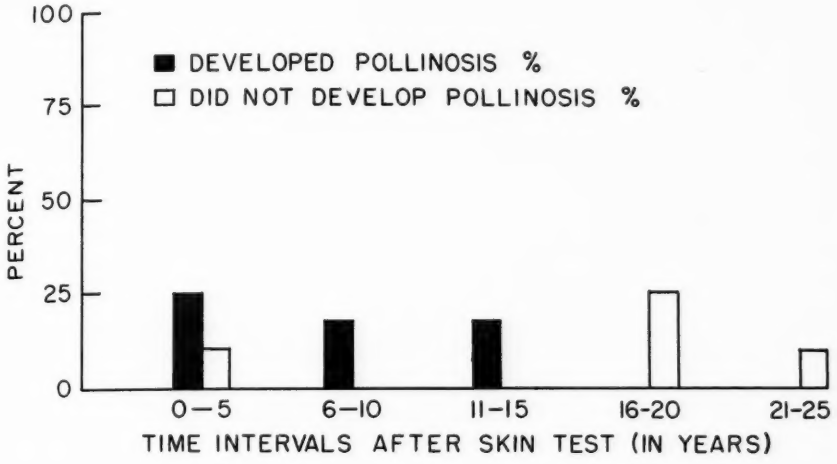

Fig. 4.—Age group 11 to 15 years.

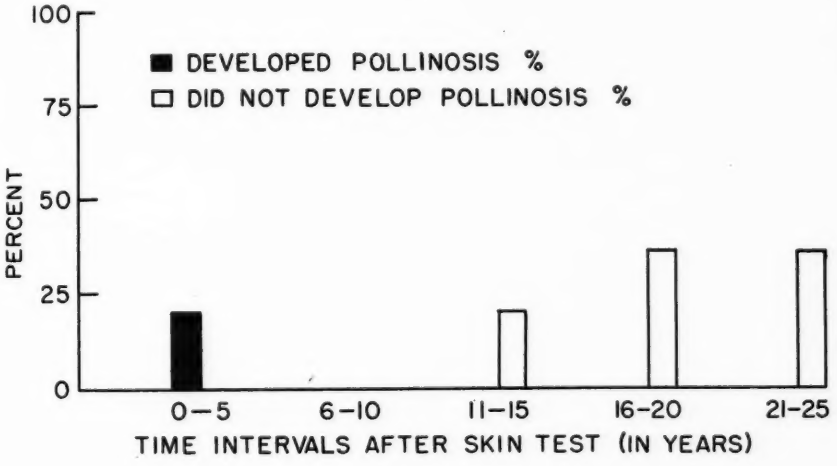

Fig. 5.—Age group 16 to 20 years.

the figures to be entirely adequate, all of these patients would have to be followed for the duration of an average lifetime to determine how long they might go without developing pollinosis. For the present, we can only estimate, on the basis of the facts given, how long the average patient will go without developing symptoms.

Of the thirty-two patients who did not develop pollinosis, eight (25 per cent) were observed for twenty-one to twenty-five years, nine (27 per cent) for

sixteen to twenty years, seven (23 per cent) for eleven to fifteen years, three (10 per cent) for six to ten years, and five (15 per cent) for zero to five years. Again, these figures must be interpreted with caution, since they are dependent

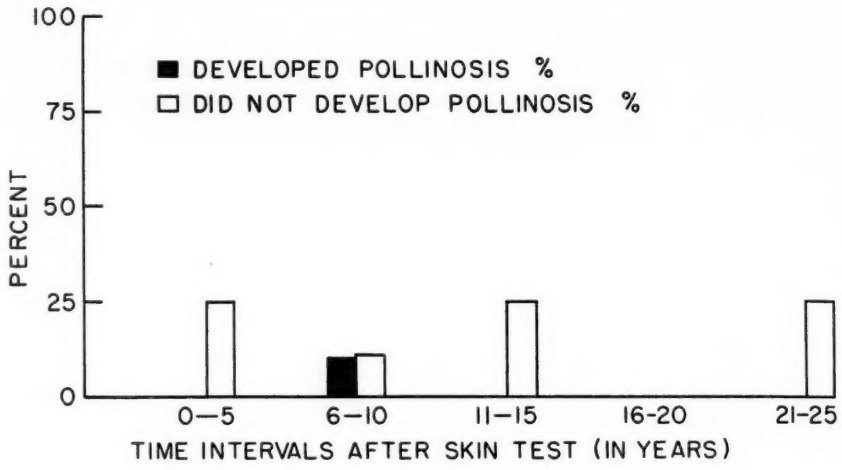

Fig. 6.—Age group 21 to 40 years.

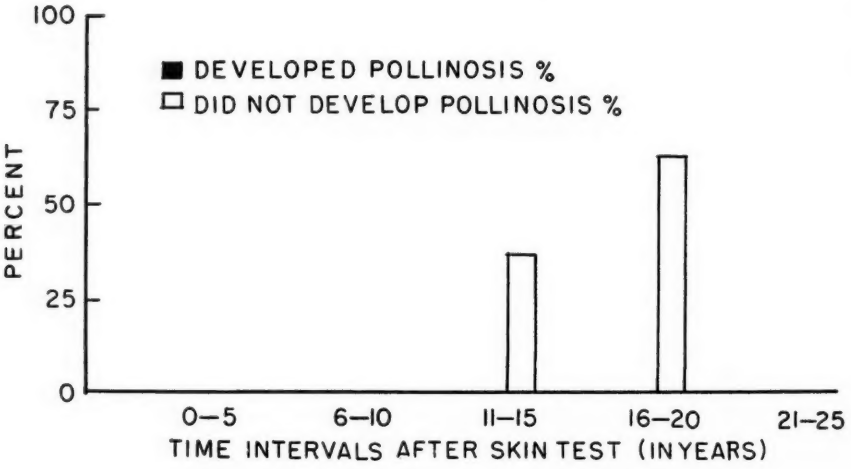

Fig. 7.—Age group 41 to 56 years.

on the patient's age at the time of skin testing and on the length of follow-up. The figures indicate that if pollinosis has not developed up to ten years after testing it is extremely unlikely that it will develop at all.

It was found that correlation of these figures with the duration of allergic symptoms, although obviously desirable, was not feasible, since the original histories were unavoidably not accurate enough for the purpose. The nature of the allergic disease often could not be determined from the one or two visits which the patient made to the office. The duration of the allergic disease was often noted in general terms, such as "all his life," "many years," or "since

childhood.'' This information would be retrospective, since it was not specifically sought for this purpose at the original visit. Because such figures would only be misleading, they were not included.

Of further interest is the fact that, of the sixty-eight patients, thirty-two were males and thirty-six were females. Sex distribution varied somewhat by age group, but the numbers in various age groups were insufficient to make a valid statistical correlation. From these figures, it is our feeling that there is no particular relationship between sex and the problem being reported.

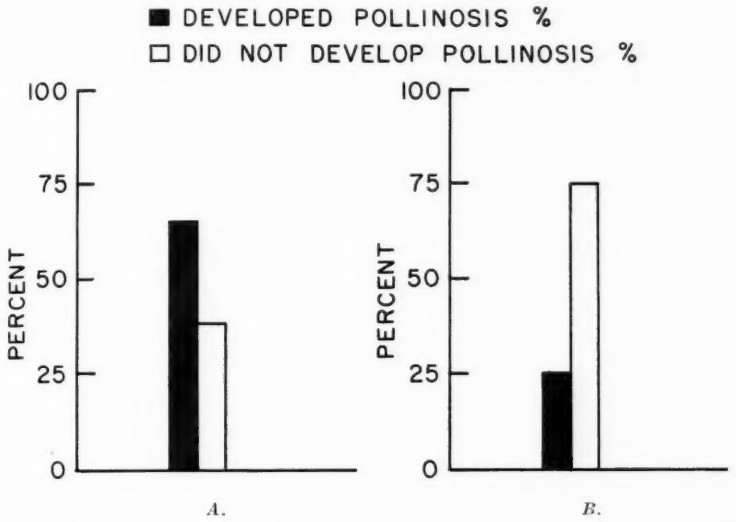

Fig. 8.—*A*, The outcome for all patients 16 years of age or under (at the time of skin testing). *B*, The outcome for all patients 16 years of age or over (at the time of skin testing).

Sixty-eight scratch tests were done, and twelve intradermal tests were done in those patients whose scratch tests were negative. These tests were distributed randomly, and there was no relationship between development or failure of development of pollinosis and the type of skin test done. Over the twenty-six years of this study, several persons have done the skin testing. The results, however, have been read by a physician in every instance, and most of them have been read by one of us (J. G.). The technique of the tests also has varied somewhat over the years, but at no time was an intradermal test done unless a preceding scratch test was negative. Most of the time the Hill scarifier has been used, and most of the tests have been done by only a few persons during the twenty-six years. The influence of such changes in procedure and personnel cannot be accurately measured or evaluated but, in our opinion, for the purposes of our study, this is not an important objection.

The only work similar to this report, which we have been able to find, was that of Biederman[1] in 1935. He mentioned unpublished data from a review of records of patients at Johns Hopkins Hospital Protein Clinic. He noted that, of 154 patients with pollinosis who had positive skin tests to pollens not

involved in their current seasonal symptoms, 5.5 per cent developed such pollen symptoms the following year. He also found that this could be prevented by the injection of these pollens along with the pollens to which the patients were actually clinically sensitive.

Finally, the problem of controls should be mentioned. Allergic patients who do not have ragweed pollinosis and who have negative skin test reactions to ragweed pollen might be considered as controls. They should be contacted and questioned as to the ultimate development of ragweed pollinosis. This, however, constitutes an entirely separate and different experiment instead of a control. We feel that the present study is controlled in itself, in that we have set out to discover what becomes of allergic patients who have positive ragweed pollen skin reactions but do not have ragweed pollinosis. We believe that we have done this. Conclusions and comparisons other than those noted here cannot be drawn from this study.

SUMMARY

1. Sixty-eight allergic patients were followed for from two to twenty-four years. They had not had ragweed pollinosis initially, but had had positive skin test reactions to ragweed pollen. The purpose of the study was to discover what becomes of such patients with regard to the development of ragweed pollinosis.

2. Of the total number of patients, 53 per cent developed ragweed pollinosis, and 47 per cent did not.

3. Of the persons developing pollinosis, 88 per cent did so within ten years of the skin tests, and 64 per cent did so within five years of the skin tests.

4. The corollary to this is that those who have not developed pollinosis ten years after skin tests are highly unlikely to do so thereafter.

5. Of the thirty-two patients who did not develop pollinosis, approximately 25 per cent were observed for twenty-one to twenty-five years, 27 per cent for sixteen to twenty years, 24 per cent for eleven to fifteen years, 10 per cent for six to ten years, and 15 per cent for zero to five years. These figures are affected by the length of time the patients were followed, and must be interpreted accordingly.

6. There was no evident relationship between sex or type of skin test (scratch or intradermal) and the development of ragweed pollinosis.

7. Of the patients in this study who were 16 years of age or *over* at the time of skin testing 75 per cent did *not* develop ragweed pollinosis and 25 per cent *did* develop ragweed pollinosis.

8. Of the patients in this study who were 16 years of age or *under* at the time of skin testing, 37 per cent did *not* develop ragweed pollinosis and 63 per cent *did* develop ragweed pollinosis.

9. In view of the foregoing findings, the practice of giving injections of ragweed pollen as a prophylactic measure along with periodic injections of other

allergens to patients who have a positive skin test but who do not have ragweed pollinosis appears justified, since there is no evidence to prove that such prophylactic measures are harmful.

REFERENCE

1. Biederman, J. G.: Treatment of Allergic Patients With Added Skin Reactions, J. ALLERGY 6: 590-592, 1935.

FUNGICIDAL AGENTS IN THE TREATMENT OF ALLERGY TO MOLDS

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PITTSBURGH, PA.

THE present study deals with a determination of the efficacy of various agents reputed to be fungicidal. It was undertaken in the hope of finding a suitable, inexpensive, nontoxic, and nonstaining agent which could effectively reduce the mold content in homes of patients allergic to molds.

LITERATURE

The role of nonpathogenic fungi in the etiology of allergy of the respiratory tract has been well established.[1-9] For the most part, they occur seasonally.[10] Their growth and distribution vary with geographic and climatic conditions. Thus, wind,[11] location,[12] temperature, and humidity[13] determine the abundance of outdoor fungi in a given area. The extent and severity of allergic manifestations produced as a result of exposure to air-borne fungus spores depend, as is the case in pollen allergy, on the extent of sensitivity to these spores as well as on their quantity in the inspired air. Since fungi are ubiquitous, it follows that the air content of outdoor spores is reflected in their distribution in the indoor house dust and air.[14, 15] Richards[16] compared the occurrence, type, and abundance of molds indoors and outdoors. He finds the colony count obtained as a result of outdoor exposure higher than that obtained indoors; the same molds are distributed in the same relative proportion in both areas. He also indicates that there is a higher concentration in damp houses. He identifies the following indoor molds: *Alternaria tenuis, Aspergillus fumigatus, Cephalosporium acremonium, Cladosporium herbarium, Penicillium* (several types), and *Pullularia.* Saito[23] and Rostrup[24] report practically the same indoor molds as indicated above, while others[17] find, in similar areas, *Penicillium, Aspergillus, Cladosporium,* and *Pullularia.* On indoor sampling, Merksamer[26] and others[21] indicate, in addition to the above fungi, *Mucor, Rhizopus, Phoma,* yeast, *Penicillium* and *Aspergillus.* Prince and associates[17] and others[22] state that even under normal conditions the spore and colony count may be higher indoors than outdoors. This is especially true in barns, greenhouses, haylofts,[23] and in old houses that are dark, dusty, musty, and damp. In such areas one may find patches of molds growing on walls, leather (shoes, luggage), fabrics (woolens, cotton), wood, pillows, mattresses, upholstery, furniture, and other articles.[16, 23] These growths are

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Received for publication Feb. 3, 1958.

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**Grantee of the American Foundation for the Study of Allergic Diseases.

erroneously referred to by the layman as "mildew." They are an added source of mold spores in the house. Nilsby[19, 20] has shown that the number of mold colonies is greater in damp "nonhygienic" houses than in clean dry ones, and Rennerfelt[21] and also Swaebly and Christensen[22] found fewer colonies in clean homes than were found outdoors. Spores are easily distributed indoors by air currents as shown by Christensen,[28] who recovered them on the fourth floor of a house within five minutes after liberating them on the first floor. These spores easily reached another room located fifteen feet away from the source, even though the door was open only two inches. This permeation, infiltration, and contamination of the air from one part of a house to another take place easily through the aid of natural air currents. It would seem that occasionally such air dissemination varies to some extent with the type of mold studied.[29] Suitable culture techniques[30] are employed in the identification of these molds.

CASE REPORTS

This study was stimulated by our recent experience with three cases of respiratory allergy—two of severe perennial nasal allergy and a third of bronchial asthma and nasal allergy. The condition of these patients improved only partially with treatment. It was then realized that they were highly allergic to molds. A brief summary of our clinical findings in each case follows.

CASE 1.—The patient, a 15-year-old atopic girl, has had severe perennial and seasonal nasal allergy for the past five years. She was found to be sensitive to may inhalants (including molds) and some foods. In spite of good coopertion and adequate specific therapy, she continued to be uncomfortable, especially during the summer and fall. Positive direct skin test reactions were obtained to *Penicillium, Aspergillus, Alternaria,* and *Hormodendrum* with a positive passive transfer to the first three molds. It was then discovered that the patient lived in an old damp home. A visit to her house showed a dusty, musty attic and a basement room full of "mildew." Fungicidal agents were then used with good therapeutic results.

CASE 2.—A housewife, 35 years of age, presented clinical evidence of presistent, severe, perennial nasal allergy with polps. This condition was present over a period of seven years. She had a positive family history of allergy; she had atopic dermatitis earlier in life and showed clinical sensitivity to house dust, peanuts, and chocolate. She gave positive skin test reaction to some inhalants and foods and a marked direct positive reaction to *Alternaria, Hormodendrum,* and *Penicillium*—reactions which transferred passively. In spite of complete and adequate therapy, the patient continued to be uncomfortable, especially when she was at home. The house was located in a river valley and, therefore, was in a damp, foggy area. Exposure of plates yielded a high mold colony count. The patient experienced marked relief following the use of fungicidal agents in her house.

CASE 3.—A 16-year-old girl gave a history of bronchial asthma over a period of ten years. This condition became worse during the past four or five years, after she moved to a new location. Investigation reveals that five years ago a storage room was added to the basement of the house. This room was damp, poorly ventilated, and received little sunlight. There were two storage cabinets in this room, and these were used to store seasonal clothes. A visit to the house revealed "moldy, mildewed" patches on many articles in this enclosure. There was "mildew" on a leather golf bag, on clothes stored in the cupboards, and on the walls. The molds were freely distributed throughout the house by air currents. During the

winter, this circulation of molds was further aided by forced air heating. This patient subsequently volunteered the information that she would invariably develop a paroxysm of asthma and nasal symptoms when visiting the basement. There was marked improvement in her condition following adequate treatment of the house with effective fungicidal agents.

The realization that the three patients just described were highly allergic to molds and that the mold content of the air in their homes was high led to an investigation as to how the element of such exposure may best be eliminated.

PAST EXPERIENCE WITH FUNGICIDAL AGENTS

Various procedures have been employed in the past to reduce indoor mold spores. These usually involve an attempt to increase the ventilation in the patient's house (particularly in the basement and attic), to reduce and avoid house dust, to dehumidify the air, and to increase exposure to the sun. In many instances, these procedures either are not possible under existing conditions or are only partially effective. Some time ago, we[31] presented evidence that electrostatic air cleaners filter out of the air all particulate matter, including pollen, spores, and dust, and also that mechanical filters, although less effective, are helpful. Centrally installed electrostatic cleaners are part of the equipment of only the newer homes, however, and therefore are not generally available. Rooks and colleagues[32] find that mechanical filters and air conditioners are not very efficient in removing mold spores from indoor air. Furthermore, such procedures simply filter out the spores and do not affect the growth of molds. A great deal of work has been done with reference to the applicability and mechanism of action of fungicides employed to impregnate materials and fabrics in order to reduce their contamination with molds. Thus, Baskin and Kaplan[33] determined that plasticized vinyl-coated fabrics become variably resistant to fungi following treatment with solubilized copper-8-quinolinate and phenyl mercuric acetate. Marsh and associates,[34] Butler and Marsh,[35] and Corey and Shirk[36] report that various bisphenol compounds are effective fungicidal agents to be used locally as "mildew" preventives on cotton fabrics. Others found certain B-nitrostyrenes and some cyclohexane derivatives to be good fungicides.[37] Volini and associates[38] determined that three different derivatives of monothiouronium prevent the growth of *Hormodendrum, Helminthosporium,* and *Candida albicans.* Nitrostyrenes[39] and triacetin (glycerol triacetate)[40] are effective against pathogenic fungi as well as against *Alternaria, Penicillium,* and *Aspergillus.* Plants and leaves of woodland trees have naturally occurring fungicidal and fungistatic substances.[41, 42] It would appear that in some instances at least the mechanism of the toxic action of these fungicidal compounds is the inhibition of fungus enzymes[43] or the coagulation of protoplasm. All of these procedures, however, have limited practical clinical application, since they are not readily available for use in large areas or under any other than experimental conditions. The literature makes only casual reference to the possible use of general fumigation of houses with formaldehyde vapor,[44] a procedure which has obvious practical drawbacks.

FUNGICIDAL AGENTS EMPLOYED IN THIS STUDY

Three agents reputed to have fungicidal properties were employed in this investigation. Following is a description of each of these agents:

*Hyagen** is a 10 per cent solution of alkyl (C9 to C15) tolyl methyltrimethyl ammonium chloride containing 90 per cent of inert ingredients. This product is noninflammable, nonirritating, nonvolatile, noncorrosive, and odorless. It does not attack fabrics or other materials, but it should not be permitted to contaminate food. It is recommended that it be used as a spray.

Roccal† (10 per cent solution) is a nonmetallic organic compound, a mixture of high-molecular alkyl dimethylbenzyl ammonium chloride. This product is freely soluble in water, is colorless, and has a slight aromatic odor. It is available in a more purified form as Zephiran chloride, a 12.5 per cent solution. This product is used in operating rooms. In an aqueous dilution of 1-10,000, it inhibits the growth of *Trichophyton interdigitale* after exposure for four to six minutes.[45] Zephiran chloride has a definitely high bactericidal and bacteriostatic effect as demonstrated by its phenol coefficient for various pathogenic organisms, including pathogenic fungi.[46-49]

Trioxymethylene‡ (crystalline paraformaldehyde) is a white amorphous powder of high molecular weight. Depolymerization occurs at a temperature of 180 to 200 degrees; hence, it is a convenient source of anhydrous, gaseous formaldehyde. This product has a melting point of 120 to 130 degrees. The commercial product contains 95 per cent formaldehyde. When heated, it is converted to formaldehyde.

TECHNIQUE

This study deals with an evaluation of the fungicidal activity of the three agents just described. The study was done on the basis of the ability of these agents to interfere with mold growth as determined on exposed Petri dishes. This investigation was carried out under six different sets of conditions to determine: (1) the effect of dipping plates into or spraying them with the agents under consideration, (2) the effect of incorporating the agents into the medium, (3) the effect of spraying agents in experimental hospital rooms, (4) the effect of subliming trioxymethylene powder in such rooms, (5) the mold content of dust in the patient's home, and (6) the effect of exposing trioxymethylene in the patient's home.

Petri dishes, 180 mm. in diameter, were employed. These plates contained sterile Mehrlich's medium with sodium chloride, 75 grams per liter. Following exposure for ten minutes, the Petri dish was closed and sealed with cellophane tape. It was not moved or disturbed until ten days to two weeks later, when all of the colonies present were counted. An attempt was made to identify the more prevalent fungi. The effectiveness of the agents employed was determined by the reduction in the number of mold colonies (Figs. 1 and 2).

*Marketed by the Miami Products and Chemical Company, Dayton, Ohio.
†Marketed by Winthrop Laboratories, Inc., 1450 Broadway, New York, N. Y.
‡Available commercially.

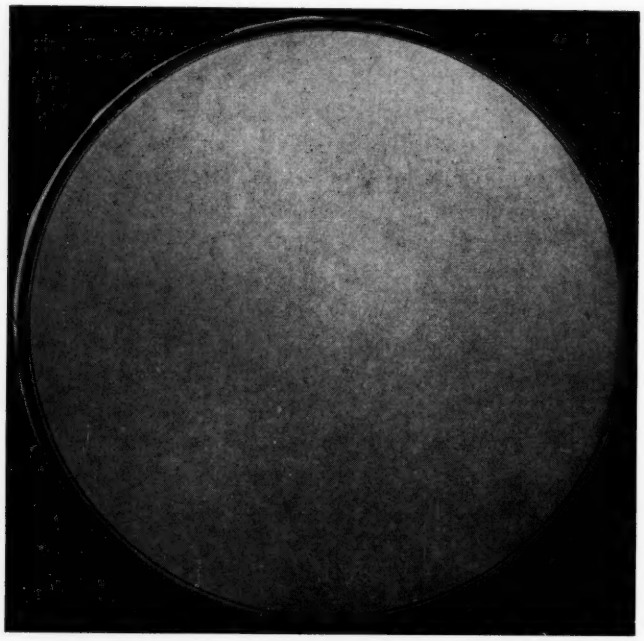

Fig. 1.—Trioxymethylene incorporated into medium prevents growth of molds regardless of method by which plate is exposed.

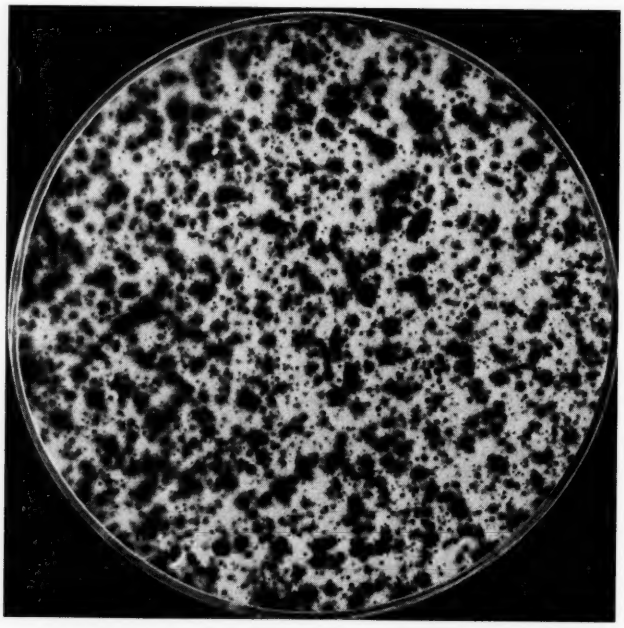

Fig. 2.—In instances where agent is not effective, the colonies are too numerous to count.

TABLE I. EXPERIMENT 1.
EFFECT ON COLONY GROWTH WHEN PLATE IS SPRAYED WITH OR DIPPED INTO AGENT
(EIGHTY-TWO PLATES)

AGENT	DILUTION	NUMBER OF COLONIES WHEN PLATE SPRAYED WITH AGENT*	NUMBER OF COLONIES WHEN PLATE DIPPED INTO AGENT*
Tap water		Too many	Too many
Sterile tap water		Too many	Too many
Normal saline		Too many	Too many
Sterile normal saline		Too many	Too many
Plain media		Too many	Too many
Hyagen	1-150	Too many	Too many
	1-300	Too many	Too many
	1-600	Too many	Too many
Zephiran chloride	1-100	0	No growth
	1-500	Only around edges	84
	1-1,000	Too many	Too many
Roccal	1-100	18	0
	1-500	218	52
	1-1,000	Too many	118
Trioxymethylene	1-10	56	16
	1-100	Too many	Too many
	1-1,000	Too many	Too many
	1-2,000	Too many	Too many

*Too many indicates that the plate was covered with such a luxuriant growth that the colonies were confluent and therefore too numerous to count.

Experiment 1 (Table I, Fig. 3). Effect of Spraying Plates With or Dipping Them Into the Agent.—This experiment was carried out in several hospital rooms. These were approximately the same size—15 feet 3 inches by 10 feet 1 inch by 9 feet 4 inches, or 1,435 cubic feet. Each room has one door and two

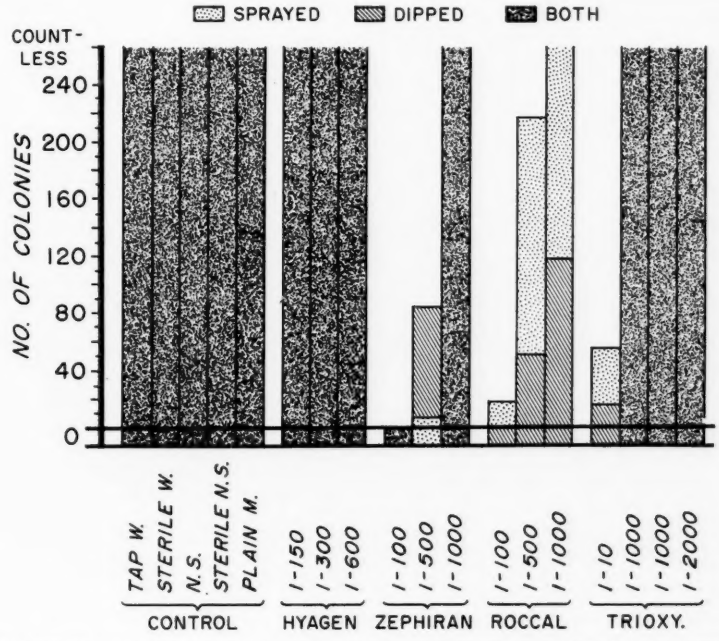

Fig. 3.—Effect on colony growth when plate is sprayed or dipped into agent. (Eighty-two plates.)

windows, and one cupboard of about 87 cubic feet projects into it. The door to the closet has a ventilating louvre, 12 by 18 inches, allowing for ventilation. A high concentration of mold spores was obtained in each of these rooms by operating an electric fan in front of several Petri dishes containing a luxuriant growth of fungi. Various dilutions were made of Hyagen, Roccal, Zephiran, and trioxymethylene. These dilutions were obtained from the concentration of the product as available from commercial sources. Trioxymethylene goes into solution with great difficulty; hence, the dilutions indicated are not always accurate. Some Petri dishes containing the sterile medium were dipped and others were sprayed with these various dilutions of the agent. The treated plates were then exposed for ten minutes in these rooms. Controls using tap water and saline, both sterile and nonsterile, as well as plain Mehrlich's medium were made. A total of eighty plates was used. The number of colonies indicated represents an average of several plates read under each set of conditions. The results are shown in Table I and Fig. 1. In the case of all controls, the growth was so abundant that there were too many colonies to permit an accurate count. Hyagen concentration as high as 1-150 had no inhibiting effect. Zephiran began to show an appreciable effect in a 1-500 dilution and permitted no growth in a 1-100 dilution. Roccal showed little effect in a dilution of 1-1,000, was moderately effective in 1-500, and was quite satisfactory in a dilution of 1-100. Trioxymethylene markedly reduced the growth when employed in a 1-10 dilution.

TABLE II. EXPERIMENT 2.
EFFECT ON COLONY GROWTH WHEN AGENT IS INCORPORATED INTO MEDIUM (130 PLATES)

AGENT	DILUTION	EXPOSED TO ROOM AIR (NO. OF COLONIES AFTER TWO WEEKS)	PLATES STREAKED WITH SPORE WASHINGS (NO. OF COLONIES AFTER TWO WEEKS)	ADDITION OF 1 C.C. OF SPORE SUSPENSION
Tap water		Too many	Too many	Too many
Sterile water		Too many	Too many	Too many
Nonsterile water		Too many	Too many	Too many
Sterile water		Too many	Too many	Too many
Plain media		Too many	Too many	Too many
Hyagen	1-3	0	3	0
	1-15	2	20	1
	1-30	16	52	15
	1-60	2	63	17
	1-100	Too many	Too many	Too many
Zephiran chloride	1-100	2	0	0
	1-500	2	11	0
	1-1,000	3	14	2
	1-2,000	9	60	80
	1-4,000	41	Too many	Too many
Roccal	1-100	0	6	0
	1-500	2	51	0
	1-1,000	8	58	1
	1-2,500	24	58	Too many
	1-5,000	85	Too many	Too many
Trioxymethylene	1-10	5	0	0
	1-20	0	0	0
	1-100	0	0	0
	1-500	0	0	0
	1-1,000	0	22	0

Experiment 2 (Table II, Fig. 4). Effect on Mold Colony Growth When Agent Is Incorporated Into the Medium.—Plates were exposed by three methods: One series of plates was exposed for ten minutes in a hospital room in which a high concentration of mold spores was liberated; another series of plates was streaked with loops containing washings from heavy fungus cultures; to the last group of plates was added 1 c.c. of a suspension of molds containing approximately 50,000 spores. A total of 130 plates was thus used. The results are seen in Table II and Fig. 2. Mold growth is completely uninhibited in the controls. In the dilutions employed, trioxymethylene is most effective. Generally speaking, the more concentrated the fungicidal agent, the greater the inhibition of growth.

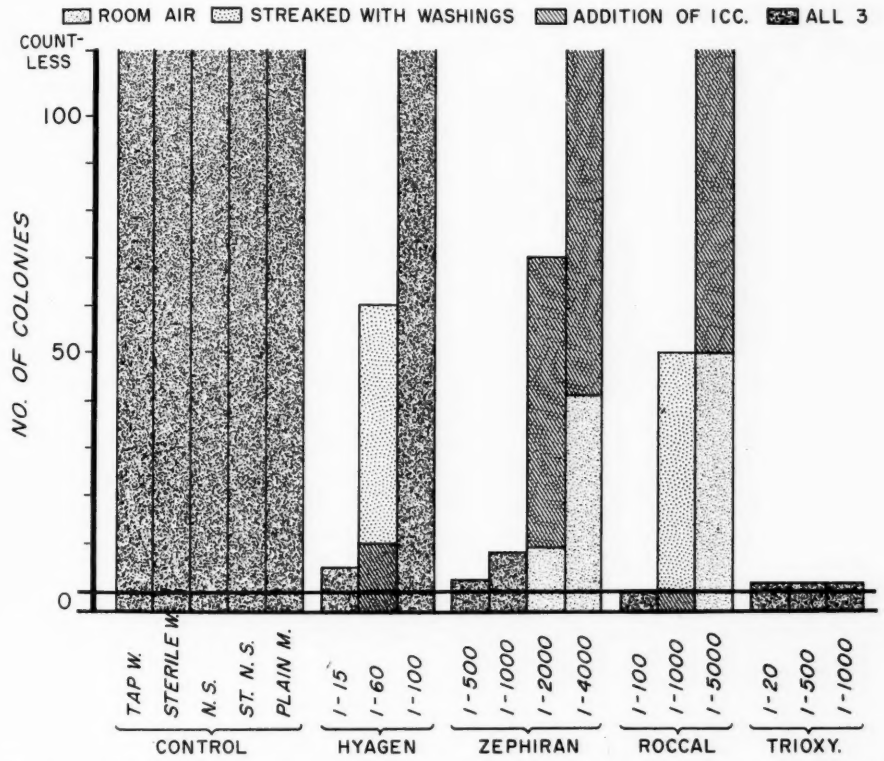

Fig. 4.—Effect on colony growth when agent is incorporated into medium. (One hundred thirty plates.)

Experiment 3 (Table III, Fig. 5). Effect on Mold Colony Growth When Agents Are Sprayed Into Hospital Rooms.—The doors and windows of these rooms remained closed. All plates were exposed for variable periods of time, as indicated in Table III. Hyagen had no effect. Roccal and trioxymethylene were about equally effective in interfering with mold growth. The count was definitely lower in instances of prolonged plate exposure, since there was thus allowed a longer period of time for fungicidal action. Zephiran was not

TABLE III. EXPERIMENT 3.
EFFECT ON COLONY GROWTH WHEN AGENTS SPRAYED INTO ROOM (28 PLATES)

AGENT	DILUTION	PLATE EXPOSURE	GROWTH IN TWO WEEKS
Control		10 minutes	Too many
Hyagen	1-15	10 minutes	Too many
		3 hours	Too many
		24 hours	Too many
Roccal	1-500	10 minutes	25
		3 hours	34
		24 hours	1
		24 hours (1 day late)*	1
Trioxymethylene	1-500	10 minutes	35
		3 hours	44
		24 hours	8
		24 hours (1 day late)*	2

*This plate was exposed for twenty-four hours one day after the room was sprayed.

employed, since its cost was prohibitive for experiment. The odor of formaldehyde was noticeable only at the time the room was sprayed. A total of twenty-eight plates were exposed in this experiment.

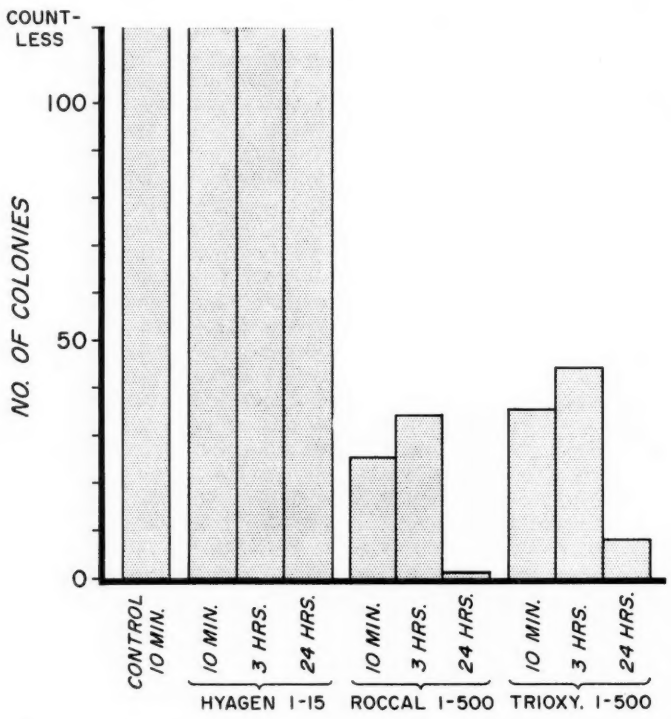

Fig. 5.—Effect on colony growth when agents are sprayed into room. (Twenty-eight plates.)

Experiment 4 (Table IV). Effect of Trioxymethylene on Mold Colony Growth When Agent Is Employed in Hospital Rooms.—Control plates were exposed as usual before trioxymethylene was used. At this point, an open jar containing trioxymethylene was placed on the floor of the closet in a hospital

room and the door was closed. The contained air space was continuous with the room air space by a louvre in the door measuring twelve inches by eighteen inches. Windows and doors were kept closed and a period of forty-eight hours was allowed for equilibrium to become established. Trioxymethylene was thus volatilized into room air. The odor of formaldehyde was detectable in the cupboard but not in the room proper with the doors and windows closed. Plates were exposed at the end of forty-eight hours when 2 of the 10 grams of trioxymethylene had sublimed. The experiment was then repeated with the doors and windows open. No attempt was made in this experiment to introduce molds into the room as was done in previous experiments. Hence, the total count is lower.

TABLE IV. EXPERIMENT 4.
EFFECT OF TRIOXYMETHYLENE POWDER ON MOLD COLONY GROWTH WHEN AGENT IS EXPOSED IN HOSPITAL ROOM (36 PLATES)

	NUMBER OF COLONIES	
	CUPBOARD	ROOM
Control windows closed	28	15
after Trioxymethylene	4	2
Control windows open	46	11
after Trioxymethylene	30	6

However, it is the relative count obtained before and after the use of trioxymethylene that is significant. The results are indicated in Table IV. Note the drop in colony count, both in the cupboard and in the rooms, with doors and windows both open and closed following the use of this agent. In the two days in which 2 grams of trioxymethylene had volatilized, the agent was eighty per cent effective in reducing the mold colony count. In this concentration, no irritating formaldehyde odor was present. No attempt was made to determine its concentration in the room air, although such techniques are available.

TABLE V. MOLD COLONIES FOUND TEN DAYS AFTER PLATING DILUTIONS OF HOUSE DUST (26 PLATES)

DILUTION	HOUSE 1	HOUSE 2
1-100	Too many to count	Too many to count
1-200	43	37
1-500	37	48
1-1,000	45	30
1-10,000	8	2

Experiment 5 (Table V, Fig. 6). Mold Content of House Dust.—This experiment was designed to indicate the mold content of the house dust in the homes of two patients (Cases 1 and 2). This house dust was diluted with sterile distilled water. As might be expected, small quantities of house dust thus obtained show a fairly high mold content indicating the necessity of reduction and avoidance of house dust. We plated 0.1 c.c. of each dilution.

Experiment 6 (Table VI, Fig. 7). The Effect of Trioxymethylene on Mold Colony Growth in Patients' Homes.—In each of these homes there was presented ample evidence of a high mold content. Hyagen was not employed in this

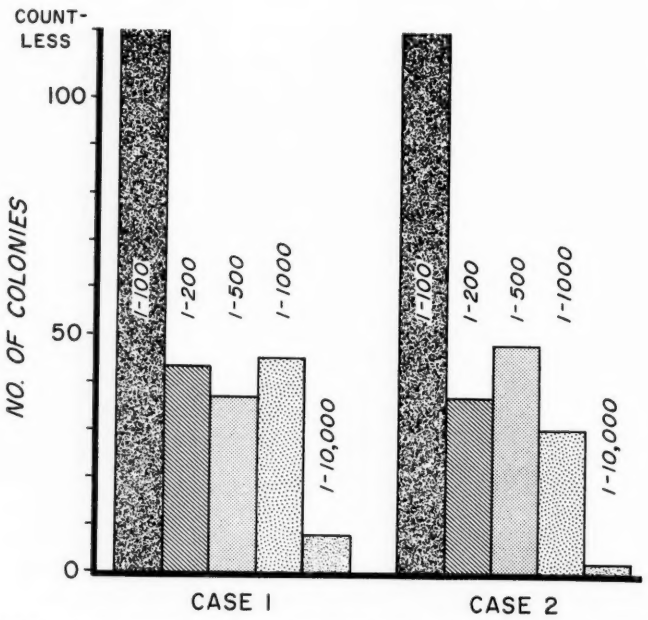

Fig. 6.—Mold colonies found ten days after plating dilutions of house dust. (Twenty-six plates.)

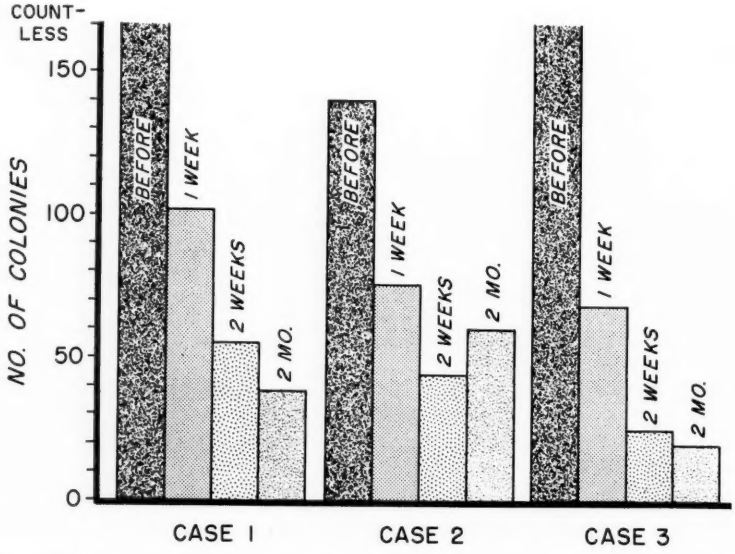

Fig. 7.—Effect of trioxymethylene on mold colony growth in basement of patient's home. (Thirty-five plates.)

experiment because its fungicidal effectiveness was doubtful in light of the results obtained in our previous experiments. Rocal, while inexpensive, has the disadvantage that its use involves spraying of home furnishings and possible food contamination. On the other hand, trioxymethylene is not toxic, is easily employed, and circulates throughout the house by natural air currents. Approximately 10 grams of the powder was placed in an open jar and located in closed storage cabinets, basement rooms, attics, and in at least one other room in the house. Multiple Petri dishes were exposed both before and at various intervals after the introduction of trioxymethylene into the house. The results are indicated in Table VI and Fig. 6. A total of thirty-five Petri dishes was employed. The molds identified as growing in homes under investigation were, in order of frequency, as follows: *Aspergillus* and *Penicillium* in the "mildew," *Alternaria, Hormodendrum, Cladosporium, Helminthosporium,* and *Chaetomium.*

TABLE VI. EFFECT OF TRIOXYMETHYLENE ON MOLD COLONY GROWTH IN PATIENT'S HOME (35 PLATES)

TRIOXYMETHYLENE USED	HOUSE (CASE 1)			HOUSE (CASE 2)			HOUSE (CASE 3)		
	BASEMENT	UPSTAIRS	CLOSET	BASEMENT	UPSTAIRS	CLOSET	BASEMENT	UPSTAIRS	CLOSET
Before	Too many	128	134	140	139	100+	Too many	92	Too many
1 week after (Sept.)	102	60	22	76	90	44	68	34	32
2 weeks after (Sept.)	55	24	10	44	32	16	24	28	40
2 months after (Dec.)	38	28	18	60	38	14	20	30	12

In the basement and in basement closets in Homes 1 and 3, before the use of fungicidal agents, there were too many mold colonies to count. There was a considerable "mildew" evident in both of these locations. After one week of exposure to trioxymethylene, there was a tremendous drop in the count in all areas. By that time about one-half of the powder placed in open jars had sublimed. There was a faint odor of formaldehyde in the basement room as well as a strong odor in the closed closets. Weeks and again two months later the count was still very low and there was no "mildew" present. The count in a dry, clean home of similar size but located higher and away from the river was considerably lower without the use of any fungicidal agents. The outdoor count in the same areas as the location of the three homes under discussion was too high to count. As stated elsewhere, following a reduction in mold content in these homes, there occurred a definite clinical improvement in the condition of the patients. One of the patients (Case 3) could not walk into the basement room because the odor of formaldehyde, while barely perceptible, was too irritating to the patient's nasal mucous membrane.

SUMMARY AND CONCLUSIONS

What are the conclusions that can be drawn from this study? The clinical course of respiratory allergy, bronchial asthma, and perennial allergic rhinitis in mold-sensitive patients is affected, as one might expect, by exposure to fungus

spores. The concentration of these spores is high in old, damp homes. A good fungicidal agent is one which must meet several requirements: it must be easily applied to living quarters; it must not be toxic; it should not be a severe respiratory irritant; it must be relatively inexpensive; and, finally, it must be demonstrated that the product is effective in abolishing "mildew" and in reducing the mold colonies obtained by proper Petri dish exposure, thus bringing about clinical improvement.

A total of 337 plates was exposed under the different conditions related in this article. Of the three fungicidal agents employed, Roccal and trioxymethylene are found to be satisfactory. Both are relatively inexpensive and commercially available. Roccal, however, must be introduced by spraying. This is easy enough in a basement room, but it offers the possibility of food contamination and may affect house furnishings. Trioxymethylene is more easily employed but, if used in large enough quantities, may produce an irritating odor. Under the conditions of our experiments, it proves quite effective in reducing the mold content of the home and is a contributory factor in the clinical improvement of mold-sensitive patients.

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Editorial

ABSTRACTS FOR THE ANNUAL MEETING FEB. 9-11, 1959

THE Program Committee of the American Academy of Allergy will meet next October to consider abstracts submitted for the scientific sessions of the Chicago meeting. The Committee has a difficult task—a task which is often made especially difficult if the abstract does not adhere closely to certain basic requirements. It might be well to take up a few of the problems which the Committee has faced in previous years.

It is usual for societies such as ours to place a definite limit on the length of abstracts. This will often pose a problem, as it may be difficult to squeeze the message into the small span allowed. Nevertheless, it is actually rare that a clear informative statement as to objective, procedure, and results cannot be made within the prescribed limits of space. Several preliminary drafts are often necessary, with careful attention to sequence and to the elimination of phrases and clauses which say less than their length would imply. Abbreviations for long, recurring terms can be very helpful. Such terms should be written out in full the first time they occur, immediately followed by the abbreviations in parentheses; for example, "Studies with sera containing skin-sensitizing antibody (SSA), heated serum containing neutralizing antibody (NA) and ragweed pollen extract (RPE) indicated that NA combines with RPE in a manner to spare SSA." The numbers of abbreviations should be limited, however, or the reader will be unable to keep them in mind. Numerals are to be preferred except at the beginning of sentences, where numbers should be written out.

In accordance with many requests, the Committee is repeating here the rules which must be adhered to:

1. The title should be brief and should clearly indicate the nature of the investigation.
2. The body of the abstract should not exceed 250 words. It should contain a statement as to the purpose of the investigation, the methods used, the results obtained and the conclusions reached. "The results will be discussed" is not a satisfactory substitute for conclusions, and such a statement usually contributes little to the abstract.

3. According to the By-Laws of the Academy, "No paper that has been published previous to the meeting or which is under consideration for publication in a journal other than the official journal of the Academy shall be presented before the Academy."
4. The abstract should be double spaced, and three copies should be submitted.
5. Abstracts should be mailed to the Executive Office of the American Academy of Allergy, 756 North Milwaukee St., Milwaukee, Wisconsin, and must be received on or before Sept. 15, 1958.

The members of the Committee have learned that, although these rules seem arbitrary, they are a necessary prerequisite for a fair and effective selection of papers. The Committee is eager to receive abstracts and feels that this set of rules might be helpful. If need for additional information arises, the President, who is the chairman of the Program Committee, and the members stand ready to help.

Erratum

In the editorial entitled "The National Institute of Allergy and Infectious Diseases" which appeared on page 85 of the January, 1958, issue of the JOURNAL OF ALLERGY, the impression was mistakenly given that a grant specifically for training in pediatric allergy had been awarded to the University of Washington. The grant was not awarded for this purpose but, rather, to support training of individuals in teaching and research in clinical allergy and basic immunology.

American Academy of Allergy

PRESIDENT'S ADDRESS

WILLIAM B. SHERMAN, M.D., NEW YORK, N. Y.

CUSTOM decrees that the president of the Academy make an address during each annual meeting. With only a half-hour of my term left, you may have thought that you had escaped. Unfortunately, you are wrong, but I will assure you that I am just as conscious as you of the long business program that we have to plow through before we can attend this wonderful dinner tonight, so I will be brief.

In one respect I have been fortunate. Our honored member, Orval Withers, addressing us as president of the College, has already said, in the Scientific Session, much that I had planned to cover in my Presidential Address. I take this as good evidence that the thinking in the College is similar to that in the Academy, and in the progressive West to that in the conservative East. What I say may be considered an extension of his remarks.

This year marks the thirty-fifth anniversary of the two societies which joined together fifteen years ago to form the Academy. These have been years of great progress. We have grown from thirty members to a membership of 1,100. We have been joined in the field by the College, an organization of equal size. During the past few years we have seen the formation of the International Association of Allergology, the Allergy Foundation of America, and the National Institute of Allergy and Infectious Diseases, all dedicated to advancing the practice of allergy. With all modesty, I think we can say that allergy has been established as an important field of medical practice.

The pioneers in the field of allergy have found that the basic sciences of botany, mycology, immunology, and chemistry lacked many of the data needed as background for their practice and have dug in to build much of their own foundation.

On the clinical levels, we have found less virgin territory. In laying out our sphere of activity we have cut across the boundaries of anatomic specialties of otolaryngology, chest diseases, and dermatology and the age barrier of pediatrics, internal medicine, and geriatrics. There have been occasional jurisdictional disputes with our colleagues in other specialties, but there is

Presented at the fourteenth annual meeting of the American Academy of Allergy, Feb. 4, 1958, Bellevue Stratford Hotel, Philadelphia, Pennsylvania.

no doubt that we have a valid and important field of activity. The question now is how are we going to develop it. Should we build a walled city to isolate and protect ourselves as specialists? Or can we mingle freely with our colleagues without losing our identity?

The answer is the same whether we are thinking on the most exalted scientific level or on the most practical economic level. No nation can progress scientifically without a free exchange of knowledge or economically without a free flow of trade. The medical specialist is equally dependent upon a liberal exchange of ideas and patients with his colleagues.

Your membership in the Academy and your attendance at this meeting are evidence of a determination to be good allergists. Our whole program is designed to further this endeavor, and I trust that it does. My purpose here is simply to remind you that a lofty structure needs a broad base in order to be stable. You cannot build a good and satisfying practice simply by pushing needles. General medicine is not a steppingstone to allergy. It is a rapidly changing field with which we must be in constant contact if we are to practice good allergy.

We cannot achieve our greatest usefulness or prestige by thinking only of allergy and attending only allergy meetings. The more we isolate ourselves from the rest of the medical profession and stick strictly to one approach, the more likely they are to consider us faddists. I find that a good many intelligent internists still think that injecting dust into patients is a strange way to cure disease. This is a matter of educating our colleagues, but there is a real danger that if we think only in terms of allergy and look at the skin tests rather than the whole patient, we may become perhaps not faddists but not the physicians we should be.

In recent years, there has been considerable and justifiable criticism of commercial allergy testing laboratories which claim to offer the same services as the allergists. In New York the allergists have been unable to convince their own county medical society to refuse advertising from such a laboratory. I am convinced that we can most effectively oppose them by being sure that our services are something that a commercial laboratory cannot offer, namely, a logical diagnosis based on a careful examination and appraisal of the whole picture rather than the literal acceptance of a series of routine skin tests. Practicing allergy should include more than doing skin tests and giving injections.

I believe that the allergist, as a physician, has another duty to the patient. This is guidance in the early diagnosis of diseases quite unrelated to allergy. Most of our patients have family doctors whom they see when they feel it is necessary, but they are in our offices far more frequently. If we show evidence of being real doctors interested in their general health, they will tell us of many symptoms which otherwise might be neglected. Naturally, we cannot attempt to treat or even completely diagnose all of these varied conditions, but a timely warning of what may prove important is a part of the practice of medicine and, incidentally, helps to maintain reciprocity in the exchange of patients with our colleagues.

In order to be good allergists we must be good physicians. The more general medicine we know and the more allergy we can teach to the general practitioners, the better our relationship with the men of the profession and the more effective the treatment of allergic patients.

In conclusion, I would like to express the gratitude of the Academy to the Local Committee for this wonderful meeting, and to thank the members of the various other committees for devoted duty through the past year.

428 West 59th St.

THE ALLERGIST AS A CLINICIAN

ORVAL R. WITHERS, M.D.,* KANSAS CITY, MO.

I WISH to take this opportunity to bring you greetings from the officers and fellows of The American College of Allergists and also to congratulate you upon the fine program which is being presented at this, your fourteenth annual meeting.

During the next few minutes I would like to discuss with you an important factor in allergy, namely, the allergist himself.

The allergist's approach to any allergy problem must, of necessity, be multidisciplinarian. He must think in terms of concomitant correlations and several, or perhaps many, related aspects of medicine as different as the pollen count and the patient's psychological stress, or the patient's relation to immunizing procedures and his allergy to drugs used for symptomatic treatment.

An examination of any textbook on allergy shows that the specialty is drifting farther and farther from the concept of being part of internal medicine and more and more into disciplines which can be considered part of internal medicine only the phrase is used in the widest possible sense. The well-trained empirical allergist finds that he knows more about allergy as such than does the internist and that his knowledge of the required part of internal medicine, as it infringes upon allergy, is greater than is the internist's knowledge of the allergic factors involved in any patient's so-called allergic response.

Let us examine a recent edition of a textbook in medicine. One of these is divided into successive headings as follows:

1. Functional and Organic Diseases of the Nervous System
2. Infectious Diseases and Those Due to Parasites and Insects
3. Physical Agents
4. Intoxications
5. Deficiency and Metabolic Diseases

The book then discusses the disorders referable to the digestive, the respiratory, and the excretory systems, the blood, and the vessels. Of 1,475 pages, less than eight are given to hay fever, bronchial asthma, and urticaria. Other allergic disorders are mentioned only fleetingly. A medical student who used

Presented at the annual meeting of the American Academy of Allergy, Philadelphia, Pennsylvania, February, 1958, by invitation.

Received for publication March 24, 1958.

*President of The American College of Allergists.

this text might conclude, and rightly so, that less than 0.05 per cent of internal medicine dealt with allergic patients. The book does not tell him that 10 to 20 per cent of all the persons who visit physicians' offices are allergic, even though allergy may not be the presenting complaint.

This book represents what appears to the internist's attitude toward our specialty. What is the specialty's attitude toward the internist? Any radiologist or dermatologist would find little satisfaction in this textbook, but then neither is really typically internal-medicine-minded. In this text the chest physician, the cardiologist, and the hematologist would find a just representation of the basic frameworks of their specialties, but this is not true of the allergist.

If this is how our specialty is regarded, how do we ourselves look at it? Our textbooks are not small. One of the best totals over 1,000 pages. Of these, the first 500 pages are devoted to immunology and to a discussion of antigens and antibodies, to inhalants, ingestants, injectants, infectants, contactants, and parasitic and physical agents. The second 500 pages duplicate the standard textbook with discussions of the allergic disorders of the various systems, tracts, and individual organs. There are special sections on pediatric and geriatric allergy. Our patients, therefore, are just as varied and their number is as great as those seen by the internist. Closer analysis gives us the reasons why almost any specialist in any branch of internal medicine can get the framework of his specialty from a textbook on the subject of general medicine and why the allergist cannot do so.

The clinician who practices internal medicine thinks in terms of homeostasis, that is, of the body's attempts to reach a stable state. When deviations occur, he wishes to restore the body to what is labeled "normality."

In recent years Selye's *general adaptation syndrome* has been used as a term to label a number of disorders characterized by the fact that the body does not seek homeostasis but, as you know, first responds, then adapts, and then breaks down.

The phenomena which occur in allergy—to take two examples, one naturally acquired, as pollinosis, and one induced by treatment of other disorders, as seen in drug allergy—fit into neither of these concepts.

The allergist cannot make an allergic patient nonallergic; he can only help him become less allergic. The allergist cannot adapt his patient; he can merely change him or his environment so that adaptation may not be necessary.

An allergist who does not separate himself from the internist in the philosophy of his approach finds himself thinking confusedly because he wants to be something that he is not. He wants to be an internist whose patients either get well or die. The particular type of internist who deals with chronic illnesses also thinks in terms of this frame of reference and seeks specific remedies. The internist who is not accustomed to allergic patients does not think of them as being sick, and yet there is no doubt that they are not well.

He is not accustomed to thinking in terms of the allergist faced with a patient who continually develops new and changing allergic reactions to foods or to drugs.

The allergist differs in at least three major characteristics from all other specialists:

1. The structure of allergy extends through all of medicine, and allergic disorders may mimic any organic or functional derangement, although such individual sydromes as allergic coryza or bronchial asthma are, in themselves, characteristic. Since there is no body organ, no body function, and no tissue cell in which he is not interested, the allergist must over and over again put his nose into the business of every other specialist. It takes a broad-minded, intellectually honest, allergically oriented specialist not to resent this so-called interference.

The average specialist actually does resent our attitude, for it makes him uncomfortable on at least three frontiers. First, we are planted right in the middle of a large number of fields of knowledge, both in and out of medicine. Basically may be mentioned otolaryngology, ophthalmology, gastroenterology, dermatology, endocrinology, hematology, physiology, pathology, immunology, pharmacology, toxicology, bacteriology, botany, and mycology, in addition to expert knowledge in food technology and industrial medicine, to name but a few of our fields. Second, being an expert in any one of these does not make a physician a clinical allergist. Third, since so many atopic disorders are spastic in nature, they are easily mimicked by psychogenic syndromes or triggered by them; we must all be expert in separating primary and secondary causes and effects, and we must be no less skilled in functional disorders and psychiatry than we are in our other fields of study.

During one week we may see examples of allergy affecting the hematopoietic system, the joints, the urinary tract, and the central nervous system, in addition to the protean manifestations of drug allergy and, as well, the usual syndromes of bronchial asthma, atopic eczema, and urticaria.

It is interesting to note how, during the last two decades, many allergists have become oriented psychosomatically. This does not indicate that basic allergy is, in any sense, psychologically induced. So many parts of it cannot, by any stretch of the imagination, so be labeled. Stress has the same effect upon allergic disorders than it does on any other disorder. The interesting point to make is that the greater part of psychosomatic medicine is also interdisciplinary. Physicians interested in the many-faceted approach to allergic problems are just as at home in the equally multifaceted approach to problems in psychosomatic medicine. It is equally interesting to note that the approach of many of our colleagues is the opposite to that conventionally seen. They do not say, "What psychological stress caused this phenomenon?" but "How much psychological stress will this allergic phenomenon produce and how can it be lessened so that it does not cause other psychosomatic or psychological disturbances?"

Ten years ago it was fashionable for the specialist, and especially the internist, to say, "First and foremost, an allergist must be a good internist." That was in the good old days when allergists treated hay fever, asthma, and some eczema. It is now quite obvious that the internist must be a good allergist.

2. There is another great difference between allergists and their fellow specialists. During the last forty to fifty years, the internist has unfortunately moved from the patient to the laboratory. The literature of internal medicine is being supplanted by laboratory procedures. The internist is being exhorted to look at the whole patient and not to regard the lungs as appended to the skeleton, and a case of pneumonia as requiring an antibiotic agent which may well affect the lungs but may also have other effects in other parts of the body. The internist is caught up with fluoroscopy and roentgenology, with the sphygmomanometer and the electrocardiogram, the electroencephalogram and the ballistograph. He looks at basal metabolic rates and measurements of many aspects of blood chemistry. These techniques and the need to specialize, for instance, in cardiac catheterization or radioactive iodine uptake, have further partitioned internal medicine.

Sometimes some of us feel a little insecure because we do not have such protective techniques to fall back upon. Everyone cannot gastroscope without an apprenticeship. Such techniques are approached with a certain respect, if not awe. People just do not feel that way about skin tests, patch tests, inhalant, or ingestant tests. On the other hand, we are the ones who are forced to take a history. It can never be too detailed. No one else will ever ask the patient whether he feels better or worse in the church or in the theater, in department stores or at the circus. Who else would ask him not only about his own hobbies but about those of every single member of his family?

Physicians often wonder why the allergist's patients are so loyal to him and why they so often say that the allergist is more interested in them than is any other type of physician they have ever met. The patients do not realize that no other physician must ask them so many questions, and such searching ones at that. The allergist holds the position of the world's best professional question asker; only he really wants to know the conditions of work and play, hobbies and diet, details of home, and the immediate external environment. It is almost impossible to take a proper allergic history without asking personal questions in numbered degree far beyond those thought of by any other physicians.

This, by the way, probably accounts for the patient's loyalty to us. They often mistake our interest in their personal habits as a personal interest. They do not realize that, although it may be personal, it really is professional. The fact that other physicians rarely ask the same questions makes them appear more impersonal.

3. There is a third great difference which helps to define us in contradistinction to other specialists. We, more than any other group I know, so often have our diagnoses made for us. Those patients who come to us for

treatment of their internal medical complaints tell us, as they do other physicians, that they have a pain, a disturbance in function, or a localized swelling. But, between how few syndromes must be differentiate when a typically allergic patient comes into the office and says, "My nose runs every August and September," "I have hives," or "My child has eczema." And, in the more remote allergic disorders, over and over again, the diagnosis is given us, and the referring physician wants to know whether the disorder is typical or of allergic origin.

There is something else which sets clinical allergists apart from the other specialists. It is something inherent in the nature of our specialty. It often makes other conventionally thinking specialists somewhat uncomfortable. We can understand their occasional dislike for what they think is an invasion of their fields. The difference of our approach is equally clear and may make them a little impatient. They do not like the fact that perhaps we are not as firmly founded in laboratory procedures as they are. Perhaps they do not like the ubiquity of allergy but, behind and beyond this façade, there is a much more fundamental reason. Not only do we not deal with a machine, as does the roentgenologist, or with a localized organ, as does the proctologist, but we are concerned with three concepts, all of which are strange to people not acquainted with allergy.

The pediatrician may deal with the young and the geriatrician with the old, but the clinical allergist concerns himself also with a special segment of the population, namely, allergic patients. Anybody—male or female, young or old—can be our patient. Second, we must help such patients avoid, or treat them for, the effects of the harmfulness of ordinarily harmless substances. This is the greatest hurdle that patients and physicians must jump. Third, allergists must be concerned in a very special way with the typical responses that these allergens, harmless to the rest of the population, cause in the allergic patients.

The strange and anomalous position of an allergist within the structure of specialized medicine gives him particular responsibilities.

He must think of allergy first, but he must treat for allergy last. Since what he believes is so hard to accept, he must advance his concepts with undeniable and concrete scientific proofs, by statistical approaches, by reproducible results, and, whenever possible, by chemical, physiologic, or immunologic experiments.

It is not enough to say that, first and foremost, the allergist must be a good internist. Of course, he must. If he were the world's best internist, however, he would nevertheless be forced into acquiring the background knowledge of large fields of human activities which are not found in any textbook of internal medicine. He must know more about bedding and about stuffings of furniture than an upholsterer and more about compositions and adulterations of food mixtures than a food technologist. He must be able to identify pollens and know dates of pollination better than the botanist and, in addition, he must be able to recognize fungi and bacteria. He must know

the components of medications and their nonpharmacologic reactions better than the pharmacist or pharmacologist. He must know the backgrounds of hundreds of industrial processes; he must be conscious of the effects of meteorologic fluctuations. He must know all of this, in addition to background knowledge in various fields of medical specialization and of science.

Today the medical schools are responsible for the undergraduate training in allergy. Here the student learns the fundamentals of immunology and of hypersensitivity. But who is to accept the responsibility for the graduate phase of clinical allergy? In the first place, more internships and residencies should be provided in order that more physicians will be better equipped to treat allergic diseases. Also, the younger physicians should see more clinical allergy. Interns and residents often lose interest or become less proficient in dealing with problems in allergy because they are too busy caring for emergency heart and chest cases or various stomach or blood disorders. Occasionally, a patient with severe asthma may receive palliative treatment. When improvement occurs he is often dismissed without further study. Is it any wonder, then, that some physicians find it difficult to recognize or adequately treat even a mild or a moderately severe allergic disorder?

For many years the Academy and the College have accepted the responsibility of providing postgraduate instruction in allergy to any qualified physician. Such programs of postgraduate training, or short courses, are well worth while and should be continued, for up to now these have been the chief source of postgraduate instruction for the clinical allergist.

Many physicians faithfully attend these sessions and study in clinics to become proficient in our specialty. Others, however, have attended only a few courses and, without further preparation, have classified themselves as clinical allergists. Naturally, the management of allergic patients by these physicians is woefully inadequate. At present, there is no means by which a referring physician may judge the quality of allergy practiced by the allergist to whom he wishes to refer his patients.

To improve this situation, The American College of Allergists has decided to advance associate members to fellowship by examination. In this venture the College has no intention of acting independently of the Academy; nor does it have any desire to work separately from the American Medical Association and its Boards, so far as general certification is concerned. In no way is this examination to be considered a political substitute for certification. It is hoped that the examination for fellowship in the College will separate the physician who merely wants to treat hay fever or give "dust shots" from the one who possesses skilled knowledge in the many fields of allergy.

The College, therefore, sincerely hopes to give recognition to those physicians who are eminently qualified in the practice of allergy and thereby to raise its own standards as well as the standards of clinical allergy.

4620 J. C. Nichols Parkway.

HISTORIAN'S REPORT

THE fourteenth annual meeting of the American Academy of Allergy was held at the Bellevue Stratford Hotel, Philadelphia, Pennsylvania, Feb. 3, 4, and 5, 1958. The scientific session was preceded by a postgraduate course on Feb. 1 and 2. The total registration included 549 physicians and 149 exhibit personnel. There were 210 fellows, 202 members, and 137 guests. One hundred eighteen wives registered in the Hostess Room. The scientific program consisted of thirty-four original papers and four addresses by guest speakers whose appearance was made possible in part by a grant made by CIBA Pharmaceutical Products, Inc. Orval R. Withers, M.D., President of The American College of Allergists, also addressed the meeting. A report of the Committee on Drugs of the Research Council was made at the scientific session.

At the annual business meeting on February 4 the following officers were elected:

President:	Max Samter, M.D., Oak Park, Illinois
President-Elect:	Francis C. Lowell, M.D., Boston, Massachusetts
Vice-President:	Jerome Glaser, M.D., Rochester, New York
Secretary:	Bram Rose, M.D., Montreal, Canada
Treasurer:	George I. Blumstein, M.D., Philadelphia, Pa.
Historian:	Homer A. Howes, M.D., Detroit, Michigan
Member of Executive Committee:	Vincent J. Derbes, New Orleans, Louisiana

The following members were advanced to fellowship: Harold Bedell, M.D., Samson Fisher, M.D., Maurice Hillman, M.D., Louis Mamelok, M.D., Samuel E. Rynes, M.D., Charles B. Shuey, M.D., Alan H. Sorrell, M.D., Jay Spiegelman, M.D., John R. Talbot, M.D., Albert H. Unger, M.D., and William I. Weiss, M.D.

The following were elected to membership: Norberto Acevedo, Samuel D. Allison, Reginald G. Allman, Harry S. Andrews, Murray C. Arkin, John A. Arkins, Robert B. Beede, Paul Brais, Milan L. Brandon, Clifton Brooks, Elizabeth L. Brown, Robert Canaan, Van V. Chambers, Leighton E. Cluff, Norman K. Cohen, William P. Coleman, John Colen, Thomas N. Corpening, Homer Crandall, Vernon D. Cushing, Fred D. Droege, Norman Epstein, George S. Frauenberger, Samuel O. Freedman, Oscar Frick, Thomas W. Fyles, Sidney Gelman, Marvin Gershenfeld, Joseph E. Ghory, Leonard S. Girsh, Syrene Goldberg, Sanford E. Goldzier II, Daniel H. Goodman, George P. Graf, Frank S. Greenslit, Vickey C. Halloran, C. Marcus Hanna, Charles A. Hannigan, Roy Hecht, Glen Heidepriem, Eugene A. Hildreth, Woods Howard, Benjamin A. Johnson, James H. Johnson, Jerome M. Korn, John D. Krafchuk,

Harold I. Lecks, John M. Lesesne, Sam M. Mackoff, Wm. W. G. Maclachlan, Charles D. Marple, Joseph M. Mattimore, Eleanor E. McGarry, Leo N. Meleyco, Francisco R. Mendizibal, Howard D. Morgenbesser, Hyman R. Morris, Eldon L. C. Muttitt, Philip S. Norman, Harold S. Novey, T. S. Painter, Jr., Roy Patterson, William J. Pflum, Herman H. Pinkerton, Viola T. Raybin, Agile Redmon, C. Bruce Rigg, Milton A. St. John, Allen L. Schwandt, Tillie Schwartz, Henry Sherwood, Jeanne M. Smith, Jack Soiefer, Lester Stroh, Donald L. Unger, Thomas J. Vecchio, Claribel Westermeyer, Derek M. Wyse, and Bernard M. Zussman.

Elected to foreign membership were Carlos B. Cagnani, Argentina; Samuel Z. Kantor, New York; Peter C. P. Waugh, Australia; and Joao Ferreira de Mello, Michigan.

The following were elected to affiliate fellowship: Dr. J. M. Ales Reinlein, Spain; Kenneth L. Burdon, Ph.D., Texas; Dr. Karl Hansen, Germany; Dr. Walter Kikuth, Germany; Dr. Friedrich Klinge, Germany; Dr. Erich Letterer, Germany; and Alec Sehon, Ph.D., Canada.

The new resolutions adopted were as follows:

To donate $2,500.00 to the Allergy Foundation of America to aid in the publication and distribution of a booklet entitled *The Skin and Its Allergies.*

A committee was appointed to re-examine the administrative function of the Academy, the educational activities, and the adequacy of the Constitution and By-Laws.

On February 2 the Philadelphia Allergy Society were hosts at a cocktail party and reception. The Schering Corporation gave an informal cocktail party and reception on February 3. The President's Dinner was held on February 4 at the Union League Club and the entertainment was provided by the Orpheus Club of Philadelphia.

Throughout the meeting the Hostess Committee, under the Chairmanship of Mrs. Merle M. Miller, provided many occasions of interest for the visiting wives.

The fifteenth annual meeting will be held Feb. 9, 10, and 11, 1959, at the Morrison Hotel in Chicago, Illinois.

Respectfully submitted,

HOMER A. HOWES, M.D., *Historian.*

Announcements

Residency in Pediatric Allergy

Childrens Hospital, Columbus, Ohio, affiliated with the Ohio State University College of Medicine, offers a one-year residency in pediatric allergy to candidates with two years' accredited residency in pediatrics. Address correspondence to John H. Mitchell, M.D., Division of Allergy, Ohio State University, Columbus, Ohio.

American Academy of Allergy
1959 Annual Meeting

The 1959 annual meeting of the Academy will be held in Chicago, Illinois, Feb. 9, 10, and 11, at the Morrison Hotel. The Morrison has excellent facilities for exhibits and meetings and is well located in downtown Chicago.

Third International Congress of Allergology

The third International Congress of Allergology will be held in Paris, France, Oct. 19 to 26, 1958. The Congress is sponsored by the International Association of Allergology, under the presidency of Dr. Samuel M. Feinberg, Chicago, by invitation from French Allergy Association. The program will include symposia on asthma and emphysema, antibodies, recent clinical advances, biochemical aspects, autoimmune reactions, atopic dermatitis, and socioeconomic aspects. There will be many participants of international renown, including such authorities as Sir Henry Dale, Forsham, Schild, Sulzberger, Löffler, Kabat, Good, Dixon, Chase, Jimenez-Diaz, and Pasteur Vallery-Radot. Short sectional papers will also be presented, and small round-table luncheon conferences will be led by authorities in several fields.

A postcongress tour has been also arranged to include visits to Vienna, Florence, Rome, Madrid, etc.

Your registration fee will include reception at the Louvre Museum, an evening at the Paris Opera House, a cockfail party at the Medical School, banquet excursions, and other entertainment. There will be special events for the ladies.

For registration and Congress information, write to Dr. B. N. Halpern, 197 Boulevard St. Germain, Paris VII, France. For travel plans and information regarding a chartered flight write to Thos. Cook and Sons, 37 So. LaSalle St., Chicago, Illinois.

Books Received

How to Write Scientific and Technical Papers. By Sam F. Trelease. Baltimore, 1958, Williams & Wilkins Company. 185 pages. Price, $3.25.

Pharmacologic Principles of Medical Practice. By John C. Krantz, Jr., and C. Jelleff Carr. Fourth edition. Baltimore, 1958, Williams & Wilkins Company. 1313 pages. Price, $14.00.

Allergy in Pediatric Practice. By W. B. Sherman and Walter R. Kessler. St. Louis, 1957, The C. V. Mosby Company. 296 pages. Price, $9.25.

Dangerous Properties of Industrial Materials. By N. Irving Sax, Assisted by L. J. Goldwater, W. B. Harris, J. H. Harley, J. J. Fitzgerald, and M. S. Dunn. Reinhold Publishing Corp., New York, and Chapman and Hall, Ltd., London, 1957. 1467 pages. Price, $22.50.

Induced Delusions: The Psychopathy of Freudism. By Coyne H. Campbell. Chicago, 1957, Regent House. 189 pages. Price, $4.00.

Ciba Foundation Colloquia on Ageing. III. Methodology of the Study of Ageing. By G. E. W. Wolstenholme and Cecilia M. O'Connor. Boston, 1957, Little, Brown & Company. 202 pages, 47 illustrations. Price, $6.50.

The Story of Peptic Ulcer. Conceived by Richard D. Tonkin. Characterized by Raymond K. Hellier. Philadelphia and London, 1957, W. B. Saunders Company. 71 pages. Price, $2.25.

Ciba Foundation Colloquia on Endocrinology. XI. Hormones in Blood. By G. E. W. Wolstenholme and Elaine C. P. Millar. Boston, 1957, Little, Brown & Company. 416 pages, 74 illustrations. Price, $9.00.

Fundamentals of Immunology. By William C. Boyd. Third edition. Interscience Publishers, Inc., New York, Interscience Publishers, Ltd., London, 1956. 776 pages. Price, $10.00.

Preventive Medicine for the Doctor in His Community: An Epidemiologic Approach. By Hugh R. Leavell and E. Gurney Clark. Second edition. New York, Toronto, London, 1958, McGraw-Hill Book Company, Inc., The Blakiston Division. 689 pages. Price, $10.00.